

"I DON'T LIKE SPINACH!"

It takes more seventy than many mothers can command to force spinach upon a tearful child. Yet careful menu planning is needed to make up the 12 mg. of iron required daily. Leichenring and Flor, as an example, found that children's diets planned to contain 5 and 8.5 mg. iron actually supplied only 3.25 and 0.5 mg., respectively, although the diet was designed to provide a high iron intake and included such foods as misuns, carrots, graham bread, prunes, lettuce, beef, and egg.¹

PABLUM *tastes good*

AND IS 566% RICHER IN IRON

PABLUM is a food that children really like and take willingly. Added to this virtue, it supplies *known* amounts of iron—more than any other food of equal caloric value! This unique pre-cooked cereal contains 566% more iron than fresh spinach with an iron content of 36 mg.² (The U. S. Dept. of Agriculture reports an even lower average for spinach—2.5 mg.³) When included in the child's daily diet from the third month on, Pablum is a valuable prophylactic against nutritional anemia. Besides the hemoglobin-building element, iron, Pablum contains copper and substantial amounts of calcium, phosphorus, and vitamins A, B, E, and G. Abundant, too, in calories, proteins, fat, and carbohydrates.

^{1,2} Bibliography on request

For a Delicious Cereal Just Add Hot Water or Milk (hot or cold)—Pablum Requires No Cooking

MEAD JOHNSON & CO., Evansville, Ind., U.S.A. *Pioneers in Vitamin Research*

Pablum consists of wheat-meal, oatmeal, cornmeal, wheat embryo, yeast, alfalfa leaf, and beef bone. Supplies vitamins A, B, E, and G, and calcium, phosphorus, iron, copper, and other essential minerals.



³ Supplied in 1 lb. cart. net wt. 1 lb.

Please do not request sample card when requesting samples of Mead Johnson products. We reserve the right of preventing their reaching unauthorized persons.

MEAD'S VIOSTEROL in HALIBUT LIVER OIL 250 D

economical, efficient
for vitamins A and D

TO HALIBUT liver oil which conforms to standards in New and Non official Remedies and which has been adjusted* to contain not less than 32,000 vitamin A Units (U.S.P.X) per gram is added sufficient viosterol (activated ergosterol) of previously determined vitamin D value to assure a vitamin D potency of not less than 250 D (or 3,333 Steenbock units per gram)

HIGHLY POTENT IN VITAMIN A

Ten drops of Mead's Viosterol in Halibut Liver Oil 250 D offer approximately 8,000 U.S.P. vitamin A units as compared with 7,700 U.S.P. vitamin A units supplied by three teaspoonfuls of cod liver oil (standardized at 700 U.S.P. vitamin A units per gram)

EQUAL IN VITAMIN D TO MEAD'S VIOSTEROL

Mead's Viosterol in Halibut Liver Oil 250 D supplies the same amount of vitamin D present in Mead's Viosterol in Oil 250 D the most potent type of antirickettic commercially available. It may therefore be used for the same conditions and in the same dosage as Mead's Viosterol in Oil 250 D from which it differs in that it also supplies generous amounts of vitamin A.

Three teaspoonfuls (the average daily dosage) of standardized cod liver oil containing 40 Steenbock vitamin D units per gram offer 480 units. Ten drops of Mead's Viosterol in Halibut Liver Oil 250 D supply 830 Steenbock vitamin D units. (50 of these units are supplied by the halibut liver oil.)

From the above comparison it may be seen that for both vitamins A and D ten drops of this product compare more than favorably with cod liver oil in dosage of three teaspoonfuls, a quantity about fifty times as much.

This results in two practical advantages: (1) In cases of fat intolerance, obesity, pregnancy and premature infants the small amount of fat in the average dose of Mead's Viosterol in Halibut Liver Oil 250 D may be given without gastric disturbance. (2) In cases where a more-than-average

dosage of vitamin D or/and vitamin A is indicated, it is possible to push the dosage of this product without fat intolerance whereas more than four to five teaspoonfuls of cod liver oil daily are usually impracticable.

BIOLOGICALLY ASSAYED

The standard of potency for vitamins A and D in Mead's Viosterol in Halibut Liver Oil is rigidly maintained by constant bioassay. Mead Johnson and Company are fortunate in having a research laboratory with long experience in bioassays. Their background in this field extends to pioneer work with cod liver oil and viosterol.

INDICATIONS

Vitamin A Deficiencies For such acute deficiencies of vitamin A as xerophthalmia, xerosis, and hemeralopia, Mead's Viosterol in Halibut Liver Oil, when given in proper dosage, is a specific.

Since vitamin A has been held to be of value in maintaining the integrity of the mucous membranes and hence to be a safeguard against the invasion of pathogenic bacteria, Mead's Viosterol in Halibut Liver Oil would seem to be indicated in cases in which it is desired to provide an aid in building up general resistance to body infection. At the present time, vitamin A cannot be regarded as "the anti-infective vitamin."

Vitamin D Deficiencies Since vitamin D is capable of raising either the serum calcium or the serum phosphorus, depending upon which is in low concentration, Mead's Viosterol in Halibut Liver Oil is indicated where such disturbances of mineral metabolism arise. Where a rapid-acting calcifying agent is required and gastric disturbances must be reduced to a minimum, it is unsurpassed.

Mead's Viosterol in Halibut Liver Oil may be administered for all purposes in which Mead's Viosterol has proved itself valuable and has the additional advantage of offering generous amounts of vitamin A.

economical for vitamin A:

Mead's Halibut Liver Oil
(without viosterol)

economical for vitamin D:

Mead's Viosterol in Oil
250 D

*The addition of other fish-liver oils from one or more of the following fish: Cod, salmon, halibut, sardines, mackerel, and herring. (This is necessary because halibut liver oil varies greatly in its vitamin A potency at different seasons of the year.)

MEAD JOHNSON & COMPANY, Evansville, Indiana

Please enclose professional card when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons.

The "constitutional tendency in rickets" Important because it explains why some infants develop normally and others cannot build the right kind of bones and teeth unless they are kept on a potent source of Vitamin D such as Viosterol!

● " There is a definite constitutional tendency to rickets, quite apart from diet, hygiene and growth, say Drs Alfred F Hess and S N Blackberg (Am J Physiol 102 8, Oct 1932)

'Among infants receiving the same diet and the same care, some develop normally whereas others develop moderate or even a marked degree of rickets

For infants whose *special* susceptibility to rickets is high, an extremely potent anti-rachitic may be used routinely. These infants often fail to receive enough protection from milder measures. Imperceptibly at first, noticeably after a few months, they develop disorders of bones and teeth which may become a lasting liability

The physician who has had wide experience with rickets is often able to recognize this tendency before the disease is fully developed. Frequently he spares infants more

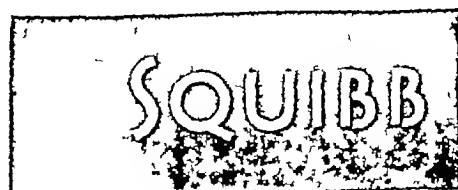
serious forms of rickets by prescribing promptly as potent a source of Vitamin D as is available for use routinely—*Viosterol in Oil 250 D*

This effective agent has many features to recommend it as a prophylactic for the baby constitutionally subject to rickets

Rapid calcifying action—The large amount of Vitamin D supplied by Viosterol brings about a prompt response in mineral metabolism. This is because of the high potency. Viosterol supplies 250 times as much Vitamin D as the standard cod liver oil defined by the Wisconsin Alumni Research Foundation

Drop dosage—Viosterol in Oil 250 D is convenient and easy to give. Babies readily tolerate the few drops needed to be effective

Less expensive—Some other anti-rachitics

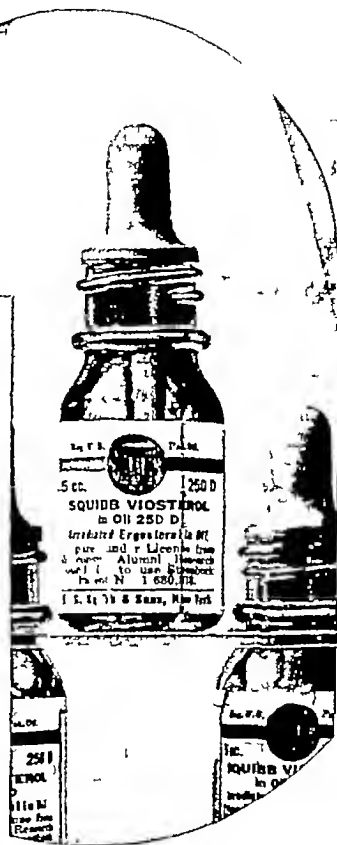


Squibb Viosterol In Oil 250 D—An extremely potent and dependable source of Vitamin D for the baby who needs special protection routinely!

as potent in Vitamin D as Viosterol, supply additional factors as well. Therefore, they cost more to give routinely. Where economy must be considered the physician will probably prefer to prescribe a source of Vitamin D alone—Viosterol in Oil 250 D!

*Squibb's the kind you will
want to prescribe*

E. R. Squibb & Sons specially protect their Viosterol in Oil 250 D! By an exclusive method of preparation they keep the high vitamin content from deteriorating. They select a purified vegetable oil for the solution. They charge it with carbon dioxide and package it under anaerobic conditions to prevent deterioration in vitamin value. The preparation reaches the physician as potent as when it was biologically tested. This helps to ensure uniform results. Always have your patients ask for *Squibb's!*



VIOSTEROL
IN OIL 250 D

MELLIN'S FOOD

IS A CARBOHYDRATE—
and more

It contains 58.9% maltose and
20.7% dextrins

It contains 10.3% protein, ex-
tracted from the wheat and
barley which are its chief in-
gredients

It contains 3.9% ash

It tends to promote normal
bowel action

MELLIN'S FOOD COMPANY

Boston, Mass

Literature and Samples of
Mellin's Food Gladly Sup-
plied — to Physicians Only

*Mellin's Food. Produced by
an infusion of Wheat Flour,
Wheat Bran and Malting
Barley admixed with Potas-
sium Bicarbonate—contain-
ing essentially of Maltose,
Dextrin, Protein and Min-
eral Salts.*





AFTER COD LIVER OIL ... WHAT?

Bond Bread

A rich source of vitamin-D*

WHEN the prescription for infants of vitamin D in the form of cod liver oil, viosterol, or vitamin D milk is discontinued isn't it important that some other source of vitamin D be made available? Foremost nutritionists agree that extra vitamin D is of value to adults also.

If our studies and those of Mrs. Mellanby are as sound as we believe they are they will afford evidence that in temperate regions people of all ages should take some source of vitamin D.

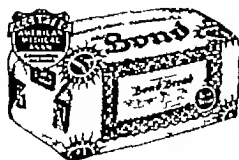
It has been our experience over a period of many years that infants and children suffering from a lack of vitamin D have lowered resistance against infection. This decreased resistance has been observed by the majority of the outstanding pediatricians in both the United States and Canada. —Dr. E. V. McCollum

Such results (referring to other research) tend to support the impression of the value of vitamin D as a food constituent for the adult. When the vitamin is supplied in moderate amounts in connection with either a high calcium low phosphorus rachitogenic ration or a low calcium low phosphorus ration calcium and phosphorus are conserved to a remarkable degree. —*Journal of American Medical Association* May 27 1933

As one of the necessary elements in building and maintaining strong bones and sound teeth an extra, easily available source of vitamin D should be valuable. What daily food source fulfills these requirements better than Bond Bread?

Bibliography on request. For further information address DR. J. G. COFFIN Technical Director GENERAL BAKING COMPANY 420 Lexington Avenue New York City

*Bond Bread contains vitamin D in the proportion of 93 Steenbock units to each pound of bread.



Bond Bread

**Also Bond Bakers Wheat Bread
Are both rich sources of Vitamin-D**

Effective LAXATIVE MEDICATION

Sodium Glycocholate..... $\frac{1}{4}$ gr
Sodium Taurocholate..... $\frac{1}{4}$ gr
Phenolphthalein..... $\frac{1}{2}$ gr
Extract Cascara..... $\frac{1}{2}$ gr
Aloin..... $\frac{1}{8}$ gr

TABLETS

OXIPHEN



Oxiphen Tablets are particularly useful in habitual constipation because they produce gentle, yet effective laxative action throughout the intestinal tract, stimulating activity of both the secretory organs and the intestinal musculature. They may be used over extended periods without losing their

effect, and without an increase in dosage and, as normal function is re-established, the dosage may be gradually withdrawn without a return of the condition. The formula contains no toxic drugs, and does not produce the "cathartic habit."

The Oxiphen formula combines the hepatic stimulant and chologogue action of the bile salts ("the only reliable chologogue known"—Cushny) with the tonic laxative effect of cascara, the simple laxative action of phenolphthalein and the stimulant action of aloin on the colon. Kindly use the coupon for literature and clinical sample.

PITMAN-MOORE COMPANY

Indianapolis

PITMAN MOORE COMPANY, Indianapolis

(JP-12-33)

You may send me a sample of Oxiphen Tablets for clinical use

M.D.

Address _____

City _____

State _____

SMA The Only Antirachitic Breast Milk Adaptation

SO SIMPLE

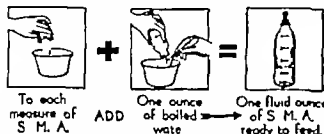
that even Mrs. _____ *can prepare it properly

SO SIMPLE

that Mrs. _____ †will thank you for sparing her
much worry and trouble

(† N. doubt you can supply names from your practice.)

ANYONE CAN FOLLOW THESE SIMPLE INSTRUCTIONS



This proportion remains unchanged. As the infant grows older you merely increase the quantity as with breast milk. (See table below)

SAVES PHYSICIAN'S TIME TOO

S. M. A. is simple to prescribe. The physician is relieved of exacting detail because he has only to increase the *amount* of S. M. A. (as with breast milk) when in his judgment it becomes necessary. The accompanying chart suggests average amounts.

The physician's time is also saved because the chances are good for excellent results under his skilled supervision.

SUGGESTED FEEDING TABLE

Infant	Total Quantity In 24 Hours In Ounces	No. of Feedings	Quantity per Feeding In Ounces
2 days	1 to 2½	2 to 3	½ to 1
3 days	2½ to 5	3 to 4	1 to 1½
4 days	5 to 7½	4 to 5	1½ to 2
5 days	7½ to 10	5 to 7	2 to 2½
6 days	10 to 12½	5 to 7	2½ to 3
7 days	12½ to 15	5 to 7	3 to 4
2 weeks	15 to 17½	5 to 7	3 to 4
4 weeks	17½ to 20	5 to 7	3 to 4
6 weeks	20 to 22½	5 to 7	3 to 4
2 months	22½ to 25	5 to 6	3½ to 5
2½ months	25 to 27½	5 to 6	4 to 5½
3 months	27½ to 30	5	5½ to 6
3½ months	30 to 32½	5	6 to 6½
4 months	32½ to 35	5	6½ to 7
5 months	35 to 37½	5	6½ to 7½
6 months	37½ to 40	5 to 4	6½ to 10

to 1 year 32½ to 40 5 to 4 6½ to 10
6 to 7 Mos. At this age it is customary to add soups and vegetables to the diet especially spinach.

* These quantities refer to fluid ounces of S. M. A. diluted according to directions.

TIME SCHEDULE

7 feedings: 6 9 12 3 6 9 and once during night.
6 feedings: 6 9 12 3 6 and 9 or later
5 feedings: 6 10 2 6 10 and 2
4 feedings: 6 10 2 6 and 10 or later
3 feedings: 6 9 12 3 and 6 or later

NUMBER OF FEEDINGS IN 24 HOURS

The number of feedings in 24 hours should likewise be the same as those allowed breast fed infants; generally started not more than seven and not less than five. However when the infant reaches the age of 6 to 7 months it is customary to replace one of the feedings with an 8 ounce meal of farina broth soup.

S M A RESEMBLES BREAST MILK

S. M. A. is a food for infants—derived from tuberculin tested cows milk, the fat of which is replaced by animal and vegetable fats including biologically tested cod liver oil with the addition of milk sugar potassium chloride and salt altogether forming an *antirachitic food*. When diluted according to directions, it is *essentially similar to human milk* in percentages of protein, fat, carbohydrates and ash, in chemical constants of the fat and in physical properties.

ETHICAL OF COURSE

If babies were all alike it might not be quite so necessary to have a physician plan and supervise feedings. However from the very beginning every package of S. M. A. has carried these instructions prominently on the label. *Use only on order and under supervision of a licensed physician. He will give you instructions.*



S M A. CORPORATION
CLEVELAND OHIO

6

S M A PRODUCES RESULTS - MORE SIMPLY, MORE QUICKLY

Anybody

*can put vegetables through
a sieve BUT THERE'S
MORE THAN THAT TO GERBER'S!*



Ordinary commercially canned vegetables, *converted* for infant feeding by straining, may be "strained vegetables"—but they aren't Gerber's

Gerber's vegetables are *special* in every sense. Grown from selected seed in selected soil,

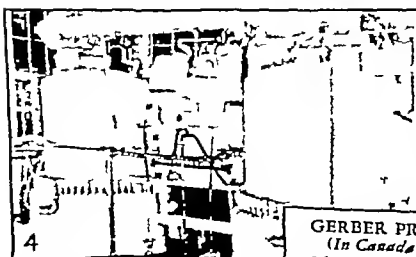
watched while growing by Gerber field supervisors, picked at the exact stage of ideal maturity, rushed crisp and fresh to the Gerber plant—Gerber's vegetables are different *to start with!*

And they are processed differently. Scientific control is established by the Gerber research laboratory, scientific methods prevent oxidation and reduce loss of vitamin values. That the resulting products are definitely superior has been confirmed by feeding experiments at Michigan State College and Columbia University, which indicate that Gerber's in minimum quantities are adequate for normal growth, whereas ordinary products have proved inadequate.

It is distinctly worth the physician's while to specify Gerber's. They remove one factor of uncertainty in infant feeding.



- 1 Hand nail and general appearance inspection twice daily
- 2 Research laboratories—controlling rigid Gerber standards
- 3 Sorting and inspection of garden fresh vegetables before washing
- 4 Vacuum cooking, conserving vitamins and minerals



Strained Tomatoes
Beans
Soup
Peas
cans
Strained Cereal
oz. cans
15c

Green Vegetables
Prunes
4 1/4 oz.
10c

Gerber's

9 Strained Foods for Baby



GERBER PRODUCTS COMPANY, Fremont, Michigan
(In Canada: Fine Foods of Canada Ltd., Windsor, Ont.)

Please send me ☐ Reprint of the article ☐ The Nutritive Value of Strained Vegetables in Infant Feeding ☐ Sample can of Gerber's Strained Cereal

Name _____ Address _____

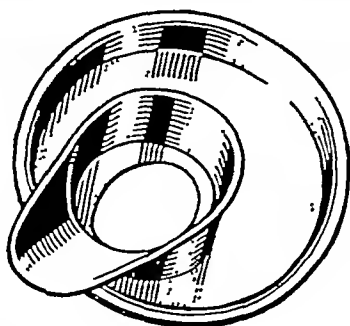
City _____ State _____

JP 12

Why CARITOL?

- 1 For ages, man has eaten certain palatable fruits, vegetables and dairy products to satisfy his hunger
- 2 His body requirements for vitamin A were thus unconsciously satisfied in greater or less degree.
- 3 The substance responsible for this vitamin A activity has recently been shown to be carotene, a yellow organic pigment [$C_{40}H_{56}$] called Primary Vitamin A by Sherman & Smith in 1930
- 4 The prevalence of latent vitamin A deficiency diseases suggests to numerous investigators that modern diets do not contain enough carotene to fully satisfy the requirements of many individuals.
- 5 The fact that carotene is normally present in various parts of the body such as the spleen blood, lymph, breast milk corpus luteum, placenta ovaries, suprarenal glands and bone marrow would seem to indicate that in addition to its activity as a vitamin, carotene itself meets other body requirements besides its conversion into the colorless product by the liver
- 6 If this deficiency is to be made up what is more natural than to supply the same palatable substance, carotene, derived from vegetables, in concentrated form?
- 7 This is now possible. A highly potent solution containing 0.3% carotene [Primary Vitamin A] in oil is offered to physicians as Smaco Caritol, available at most pharmacies.
- 8 Caritol literature may be obtained from S. M. A. Corporation, Cleveland, Ohio.





This new pouring spout converts the KARO can into a practical syrup pitcher with protective cap

NEW ...for convenience...for accurate measurement...for greater hygienic protection of KARO babies

IN KEEPING with the progressive policy of the makers of KARO Syrup, this new KARO pouring spout has been devised (1) to further safeguard the purity of KARO Syrup, (2) to make the measuring of KARO more accurate and convenient, (3) to provide insurance against contamination.

Your patients will be glad to know about this new feature. Despite the costliness of the new spout, the price of KARO remains the same.

The KARO pouring spout may be obtained without cost by addressing the manufacturer.

Year after year KARO enjoys greater acceptance by the medical profession. Its value as a practical carbohydrate in the modification of milk for infant feeding is now universally recognized.

FREE TO PHYSICIANS

KAROprescription blanks for whole milk, evaporated milk and acidified milk formulas will be provided free to physicians upon request. Write to: Corn Products Refining Company, 17 Battery Place, New York City.



NO FISHY TASTE *because* they contain the **PALATABLE** **FRUIT AND VEGETABLE FORM OF VITAMIN A**

CARITOL, for A, alone—



Caritol is a 0.3% solution of Carotene ($C_{40}H_{56}$) the palatable fruit and vegetable form of vitamin A, and therefore represents the form in which most vitamin A is naturally consumed by the human body

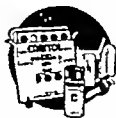
Helps Build Resistance and Promotes Growth

Caritol, by virtue of its vitamin A activity promotes growth and, as indicated by experimental studies may be an aid toward the establishment of resistance of the body to infections in general. It may be prescribed alone or with other vitamin products. There is no fishy taste or bad after taste. The cost is reasonable too. Caritol is available in 15 cc and 50 cc dropper top bottles and in capsules packed 25 and 50 to the box



Prescribe these naturally palatable vitamin products — they cost no more.

CARITOL-with-Vitamin D



Caritol with Vitamin D is the most palatable combination of vitamins A and D on the market because it contains the fruit and vegetable form of vitamin A, carotene, and a tasteless vitamin D prepared for therapeutic use by methods (Zucker process) developed at Columbia University. It is naturally palatable, not artificially flavored.

For A and D, together in Palatable Form

Caritol with Vitamin D is therefore especially recommended for patients who need both vitamins A and D but object to the fishy taste of fish liver oils and their concentrates

There is no fishy taste or bad after taste, and the cost is reasonable. Available at prescription pharmacies in 5 cc. and 50 cc. dropper top bottles and in 25 capsule boxes

Taste the carotene products yourself. Write for samples. We also offer *Smaco Cod Liver Oil* fortified with carotene and vitamin D for those physicians who prefer to prescribe cod liver oil. It is three times as potent in both vitamins A and D. Therefore one teaspoon is equivalent to three teaspoons of good grade cod liver oil. Improved flavor and minimum cost to patient. For vitamin D alone (for the prevention or cure of rickets) we offer *Smaco Vitamin D* a highly potent extract of the antirachitic principle of cod liver oil prepared by methods (Zucker process) developed at Columbia University. Ten drops equivalent in vitamin D potency to three teaspoons of good grade cod liver oil.



S M A. CORPORATION **CLEVELAND, OHIO**
"World's Largest Producer of Carotene"



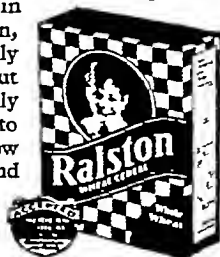
Do Youthful Patients Think You're a "GOOD EGG?"



DOESN'T it give you a "kick" to be more than just "doctor" to those young patients who are supposed to put physicians and the Spanish Inquisition in the same classification?

And aren't they a lot easier to treat successfully when they consider you a "regular fellow"?

Many physicians tell us that Ralston Wheat Cereal contributes materially in building up this "regular fellow" attitude on the part of children—especially in cases of anorexia. For Ralston, with its extra vitamin B, not only promotes normal appetites, but really tastes delicious. Naturally those child patients are glad to think you've hunted high and low for their special benefit to find something that's not only good for them but good to eat, too.



*Whole Wheat
Value—Double
Rich in Vitamin B*

Ralston Wheat Cereal is made of whole wheat (with only the coarser bran layer removed). Naturally rich in vitamin B—Ralston has been made double-rich by the addition of an extra quantity of wheat hearts. Ralston, with its abundance of the highly nutritious body-building elements, contains more vitamin B than any other cereal for growing children.

A Research Report on the new "double-rich" Ralston Wheat Cereal—and samples for testing—will be sent to you **FREE**. Use the coupon.


RALSTON PURINA COMPANY, Dept. I,
150 Checkerboard Square, St. Louis, Mo.

Please send me copy of your Research Report on the new Ralston Wheat Cereal and samples for testing.

Name _____

Address _____

This offer limited to residents of the U S



RAPIDLY GAINING FAVOR

ALERDEX - THE PROTEIN-FREE MALTOSE AND DEXTRINS

WHY IS ALERDEX PROTEIN-FREE?

● Since certain proteins are frequently the cause of eczemas and other forms of allergy it is desirable to eliminate these offending proteins from the infant diet. Cereal proteins are frequently present as contaminants in some milk modifiers. The routine use of a protein free carbohydrate in all milk modifications should help to diminish the incidence of these troublesome eczemas. Alerdex is a protein free carbohydrate developed by our Research Division to meet this need and the demand for it is steadily increasing.

A modest announcement of Alerdex a year ago found physicians ready and anxious for such a product. There is now a definite trend to use Alerdex routinely in all milk formulas.

Of course Alerdex should always be used as the carbohydrate addition with Smaco Hypo-Allergic Milks with the assurance that eczemas due to cereal protein sensitization will not be aggravated.

CHARACTERISTICS OF ALERDEX

1. Helps prevent eczemas when used routinely due to absence of offending protein.
2. Use present formulas because Alerdex has same caloric value and percentage of maltose and dextrins.
3. Does not cake on exposure to air because it is non-hygroscopic.
4. Dissolves readily in warm water or milk.
5. Shaw white, free flowing powder.
6. Inexpensive—in spite of extra processing under technical control, costs no more.

APPROXIMATE ANALYSIS OF ALERDEX

Alerdex is essentially a mixture of approximately equal parts of maltose and dextrins. It is prepared by a new thermally-controlled process of the enzymic hydrolysis of non-cereal starch, as a result of which it contains no protein contaminant.

Molality	3.0
Asb	0.5
Fat (ether str. et)	0.0
Hydrolyzed protein (N x 6.25)	0.05
Reducing sug. as maltose	50.0
Dextrins (by difference)	49.8
Level tablespoons per ounce	4
Calori 100 g level 1 tablespoon	17.6
Calori 100 g per ounce	118



Prescribe Alerdex in your own practice. For samples and literature simply attach this paragraph to your letterhead on pre-cription blank. S.M.A. Corporation 4414 Prospect Avenue Cleveland Ohio 56-123

© 1932, S.M.A. Corporation, Cleveland, Ohio

PRESCRIBE ALERDEX THE PROTEIN-FREE MALTOSE AND DEXTRINS

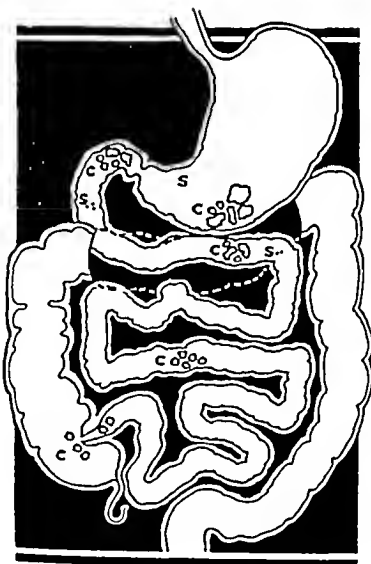
CURD TENSION

- AND INFANT FEEDING -

ITS • EFFECT • UPON • THE • ASSIMILATION • OF
FATS



BREAST MILK SIMILAC POWDERED MILK COW'S MILK



C—Cow's milk S—Similac
Schematic drawing of the relative size of the curds of cow's milk and Similac vomited by six weeks old puppies after one half hour's ingestion.

FAT has a caloric value more than twice that of either carbohydrates or protein and serves very well to make up the necessary energy or caloric requirement. Two of the important vitamins, 'A' and 'D', are associated with the fat of milk and when the diet is low in milk fat these vitamins must be supplied in some other form"¹

"When milk curdles in the infant's stomach it entangles a large proportion of the milk fat in its meshes and only such fat as lies near the surface of the curd can be reached by the digestive juices. The amount of fat in the curd depends upon the amount of fat in the milk."²

The soft, fine curds of SIMILAC, which register zero on the tensiometer, expose a greater surface area for the digestion of the fat than do the large, tough curds of fresh cow's milk

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes. Result—a more complete utilization of the food elements

¹Marriott Infant Nutrition, pg 49

²Talbot Morse and Talbot, Diseases of Nutrition and Infant feeding, pg 48

Samples and literature will be sent on receipt of your prescription blank.

SIMILAC—Made from fresh skim milk (casein modified) with added lactose salts milk fat and vegetable and cod liver oils



M & R
DIETETIC LABORATORIES, INC.,
COLUMBUS, OHIO.

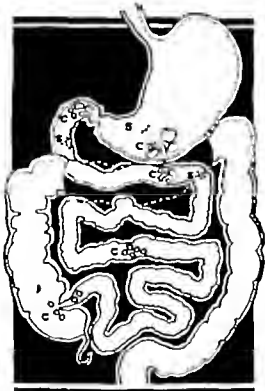
CURD TENSION

- AND INFANT FEEDING -

ITS EFFECT UPON THE ASSIMILATION OF CARBOHYDRATES



BREAST MILK SIMILAC POWDERED MILK COW'S MILK



C—Cow milk S—Similac
Schematic drawing of the relative size of the curds of cow's milk and Similac vomited by six weeks old pupples after one-half hour's ingestion.

THE curds of milk contain only a small amount of carbohydrates, sufficient, however, to be a disturbing factor in infant feeding.

"A large part of the digestion and absorption of the carbohydrates takes place in the upper part of the small intestine."

"The disaccharides, maltose, sucrose and lactose, are converted into monosaccharides through the action of enzymes secreted by the small intestine and are absorbed in the form of monosaccharides."

"When absorption is impaired, some sugar may reach the large intestine and here be attacked by the bacteria present. Sugar itself rarely appears in the stool, it being decomposed to form acids and gases."

The large, tough curds of cow's milk are more slowly disintegrated and thus more slowly release the encased carbohydrates than the soft, flocculent curds of SIMILAC.

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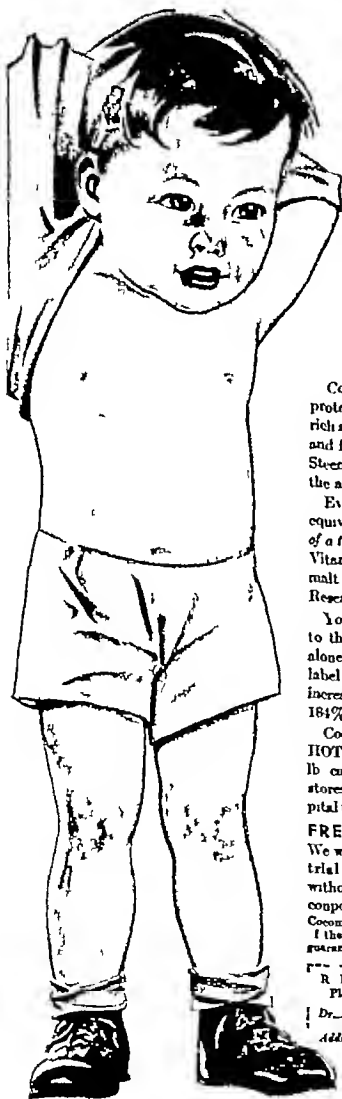
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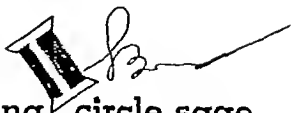
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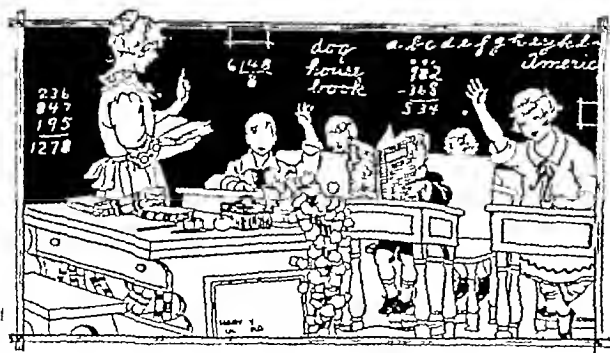
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THE Importance of Vitamins IN THE DIETARY

THE increasing recognition of the importance of vitamins in the dietary together with discoveries of hitherto unknown functions of these mysterious food components has focused undue attention upon specific vitamins and less upon others of equal importance. It is but natural that those sponsoring a product having a high potency of any single vitamin should stress the value of that one above all others.

But medical research has demonstrated that it is becoming increasingly difficult to separate definitely the functions of one vitamin from those of another. For example, investigation appears to show that vitamin D associated with calcium and phosphorus tends to prevent dental caries. It also appears that vitamin C is likewise of value in the prevention of tooth decay. It has been shown that an excess of vitamin D increases the tendency to infection unless the ingestion of vitamin A is correspondingly increased. Research has indicated that not only vitamin A but also vitamins B and G are growth promoting. In a word the sympathetic unity of action of vitamins must have the physician's careful consideration.

Further, it has been shown that there exists a definite balance between vitamins by greatly increasing vitamins A and D in diets, an otherwise adequate amount of vitamin B is made inadequate—leading to death of animals. Care should be taken not to overdose with cod liver oil or viosterol unless, at the same time, an increasing quantity of vitamin B and G are also added to the diet. As a result of new information, there is a growing tendency on the part of the medical profession to advocate the administration of vitamins in group form.

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(Dr. HENRY E. IRISH discussion of Dennett's paper *The Teaching of Infant Feeding* Arch. Pediat. Vol. XLVIII No. 4 April 1931)

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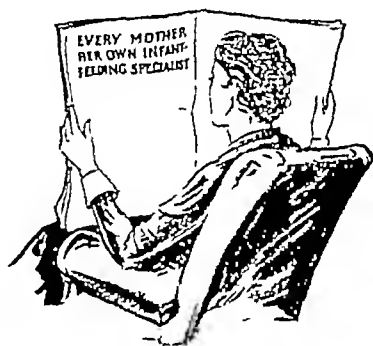


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The Journal of Pediatrics

VOL. III

DECEMBER 1933

No. 6

Original Communications

THE TREATMENT OF CHOREA BY INDUCED FEVER

LUCY PORTER SUTTON, M.D.,

AND

KATHERINE G. DODGE, M.D.

NEW YORK, N. Y.

SINCE October 1930, most of the cases of chorea admitted to the Children's Medical Service of Bellevue Hospital have been treated with fever produced by the intravenous injection of typhoid paratyphoid vaccine. We report in this paper on the results obtained in 150 cases and offer a comparison in 150 cases cared for on the same service prior to 1930. A preliminary report on the first 24 cases so treated was published in 1931.¹

The volume of literature written about chorea is tremendous and is evidence of the lack of knowledge other than clinical about the disease. Neither the pathology nor the bacteriology is definitely established. The general opinion is that chorea is an encephalitis involving the basal ganglia and that it is due to the same toxic agent as that which causes rheumatic fever. The number of different treatments used for chorea makes a long list. With certain exceptions none have appreciably shortened the course of the disease.

In 1923 Tibor von Kern² reported three children with chorea to whom he gave intramuscular injections of milk at three to five-day intervals. He felt that the course of the attacks had been shortened to three or four weeks' duration but did not attribute the results to the fever produced. Several other reports occur in the German literature on this method of treatment. In 1927 I. Somogyi³ published in an Hungarian periodical the results obtained in 30 cases. He felt that the course of the attacks was shortened to from three to five weeks. He gave the injections in the clinic and allowed the patients to go home to have the reaction. The authors who reported on the use of milk injections discussed the mecha-

From the Department of Pediatrics, New York University and the Children's Medical Service of Bellevue Hospital.

This work has been done with the help of a grant from the Josiah Macy Jr. Foundation.

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nism of the foreign protein reaction and apparently did not consider the possibility that fever might be the effective factor

In 1929, Roeder⁴ first reported on the use of nirvanol (phenyl-ethyl-hydantoin) in chorea, and since then many articles have been published, most of them reporting on rather small series of cases. Apparently the course of an attack of chorea is definitely shortened by the use of the drug, at least in those cases which show fever as a result of the drug poisoning. In a very reasonable article on this subject Pilcher and Gerstenberger⁵ state that the majority of patients who react to the drug with fever and morbilliform rash usually improve rapidly, while milder cases and those who do not react with fever and rash are not appreciably benefited. A few recent reports have commented unfavorably on this treatment, in that the authors failed to see beneficial results from the use of the drug. Here again the actual number of cases is small.

The danger of nirvanol lies in the poisoning which may result in serious complications and even death. Some such cases have been reported in the literature, and we have been told of others not reported. The complications may be nephritis, pneumonia, hyperpyrexia, or extensive and intractable skin lesions. On the other hand, Dennett and Wetchler⁶ have reported a series of 72 cases of chorea treated with nirvanol with no serious complications whatever. They feel that the drug can be given safely to children in the hospital and under competent medical supervision.

In 1930 Mas de Ayala⁷ reported the case of a child with chorea to whom he gave relapsing fever. The result was very striking, and after the fourth bout of fever the improvement was complete. This author claims to have been the first to use fever therapy in chorea. This article appeared in the Spanish literature and was not found by us until some time after it had been published. Also, we, as well as others, have observed the beneficial effect of an intercurrent acute febrile illness such as measles, typhoid, acute tonsillitis, on chorea.

Dr Nathaniel Chapman in 1818* said "The intermittents do some times cure other diseases, as gout, rheumatism, acute and chronic, chronic cutaneous eruptions are frequently cured by them, spasmodic complaints as chorea, epilepsy, asthma, hysteria, mania and especially melancholia. I have told you it is the fashion in Europe to send patients with pulmonic complaints to miasmatic countries, and you have heard of the practice being used in our own country."

*Dr Richard Kern of Philadelphia in a personal communication gives the source of this quotation as follows:

There are in existence two large notebooks written apparently by an auditor of Dr Chapman's lectures as delivered in the University of Pennsylvania School of Medicine in the year 1818. These notebooks are in longhand and are practically identical suggesting that the writer was an individual who took down Dr Chapman's lectures possibly stenographically and sold the copies to medical students.

The copy which I was able to see several years ago is one that was in the hands of a medical student who was at the University at that time and has come down to one of his descendants Dr David L. Farley of our Medical Staff.

The other copy is in the possession of the Dean of the Medical School Dr William Pepper.

Since the one factor common to treatment by milk injections, nirvanol intoxication, relapsing fever, intercurrent infections, and typhoid paratyphoid vaccine injections is the production of fever, it is difficult to escape the conclusion that it is the fever which is beneficial in chorea, rather than the instrument which produces fever.

We first started to investigate the use of fever therapy in chorea in 1929. In March of that year a boy with severe chorea was given luminal as a sedative. He became intoxicated with the drug and developed a high fever. To our surprise the chorea began to clear rapidly after a few days of fever. The symptoms which this boy exhibited were similar to those which occur in nirvanol poisoning, namely rash and fever. Since luminal had been used by us before in chorea with no beneficial effect on the disease, it seemed logical to investigate the matter of fever therapy. For about a year we tried to produce fever with typhoid vaccine intravenously but found it impossible to get continuously satisfactory fever with this vaccine. However, an occasional good febrile result occurred followed by apparent improvement in the chorea, so that we were encouraged to continue the investigation. Finally in the fall of 1930 we began to use typhoid paratyphoid vaccine, and found that we could produce fever almost at will. The reason that typhoid vaccine and later typhoid paratyphoid vaccine were chosen as the means of producing fever was that it is cheap, easily available, requires no elaborate set up and is safe. Malaria was considered, but only luetic blood was available at that time. There is also a definite mortality among paretics from the malaria itself.

A method of procedure has been developed which produces satisfactory results. It should always be kept in mind that the object of the treatment is to shorten the attack by producing fever of at least 104° F and that the vaccine is merely the means of obtaining the fever. We have found that a temperature of less than 104° F is of little use and feel that a fever of between 104° F and 106° F is the most effective.

Treatment with intravenous triple typhoid vaccine†

Aims

1. To shorten the duration of the chorea, and therefore treatment is begun as soon after admission as possible.

2. To get a daily temperature rise of 104° or over and to maintain it for as many hours as possible. Treatment being given daily until all signs of chorea have cleared. A day when the temperature does not reach 104° is a wasted day!

3. To make the children as comfortable as they can be made during treatment.

Method

1. Use New York City triple typhoid vaccine (containing 1000 million *B. typhosus*, 750 million each of Para A and B per c.c.) a tuberculin syringe, and 24 G $\frac{3}{4}$ " needle.

2. The vaccine should be boiled for three minutes before the first time it is used, and always kept in the ice box between treatments.

†Instructions developed for use of the internes on the Children's Medical Service at Bellevue Hospital.

3 First dose 0.05 c.c. TTV, undiluted, intravenously



4 Second dose is governed by the reaction of the child to the first dose for instance if the temperature the first day goes to 106° or over, repeat 0.05 c.c. the second day if it goes to $105^{\circ}\pm$ then give 0.075 c.c., and if to only about 104° then give 0.1 c.c. TTV

5 Subsequent doses are determined entirely by the reaction of the child. In general increase the dose of vaccine by a larger amount each day. The average case may take first day, 0.05 c.c., second day, 0.075 c.c., third day, 0.15 c.c., fourth day, 0.25 c.c., fifth day, 0.4 c.c., sixth day, 0.6 c.c., seventh day, 0.85 c.c.

However, this routine cannot be counted on to obtain adequate temperature elevation. A much larger increase may be necessary or

6 Second doses on the same day may have to be given. If the temperature does not reach 103° , or only one or two readings in the neighborhood of 103° are obtained, then a second dose on the same day should be given. This second dose is usually one-third to one-half the original dose of the day. For instance if the first dose of the day was 0.6 c.c. and at the end of two hours the temperature is 103.2° and fifteen minutes later is 102.8° , then 0.2 c.c. TTV should be given at this time. If the temperature has dropped below 102° , then 0.3 c.c. should be given.

Note In giving the second dose it is necessary to get it in as soon as possible after the temperature becomes stationary or begins to fall, otherwise a temperature

curve like this  instead of like this  may be obtained. When it be-

comes obvious that a second dose may be necessary, have temperatures taken more frequently than one q. hour, so that it will be known almost as soon as it begins to fall.

7 Keep the child well covered during the whole of temperature reaction. If the child becomes uncovered, temperatures do not stay up so well.

8 Treatment should be given daily unless condition of patient indicates need of a rest (severe vomiting, poor fluid intake, etc.) or unless the ward situation makes it impossible. *Never give first dose on a visiting day.* (The child may be taken out by the parents with a temperature of 104° if you do.)

9 Treatment should be given until all signs of chorea have disappeared. This is generally easy to tell in the mild and moderate cases, but may be more difficult in the severe ones. If there is much weakness and pseudoparesis present, there may be incoordination due to this weakness and to the prolonged treatment, after all signs of true chorea have cleared. When in doubt try massage and occupational therapy. The mild and moderate cases take on an average of 57 treatments and the severe cases 1015.

10 Urines should be examined by the interne daily during treatment, for albumin and red cells. In our series we have not seen anything more than a transient albuminuria, and occasional red cells. However, hematuria has been reported to us. Therefore if the urine shows more than an occasional red cell, stop treatment until the hematuria clears.

11 Occasionally, especially in severe cases, a second course of vaccine may be necessary after an interval of several days or longer. In this case we have found that the size of the first dose of the second series depends on the interval. The following is a rough guide for dosage.

Interval of 13 days—Proceed as though there had been no interval.

Interval of 47 days—Give the same dose as that given on the last day of the first series.

Interval of 89 days—It is probably best to give a somewhat smaller dose than that given at the end of the first series, although if the reaction to that dose was poor, then the same dose may be repeated.

Interval of 10-20 days—We have had no patients who have fallen into this group. To be safe the dose should probably be decreased to about one-half the previous dose at 14 days and to one-quarter at 16 days.

Interval of 20 days—Series should be started over again at 0.1 c.c.

Care of patient during reaction

1. Protein shock, with chill, severe headache, vomiting etc., generally occurs 20-50 minutes after the vaccine is given. The children are more comfortable if already hot, therefore extra blankets and hot water bottles should be given as soon as the vaccine has been given.

2. Codeine in maximum doses ($\frac{1}{4}$ to $\frac{5}{8}$ gr according to size of patient) relieves the headache to some extent. This should be given about 20 minutes after the vaccine on the first and second days of treatment, and should be given by hypodermic in thigh (to avoid a sore arm on which a tourniquet will be put the next day). After the first two days' treatment the codeine may not be necessary and it may therefore be left as an S O S order, which may be given by mouth if the child is not vomiting.

3. Vomiting usually occurs during the first two or three reactions. Therefore lunch is omitted on these days. After this, vaccine may be given immediately after the noon meal. If for any reason the vaccine is to be given at another time during the day, see that provision is made for adequate food intake at some time during the day.

4. We have found that large drinks of fluids are likely to bring the temperature precipitously down and therefore fluids should be limited during treatment. Small sips of water or fruit juice however make the children much more comfortable. Treatment of hyperpyrexia.

1. Aspirin gr 5 ice-cap to head and a drink of water are usually given if two readings above 106 at fifteen minute intervals are obtained. This should be done routinely if there is no doctor on the ward. However some of the children have surprisingly little discomfort at high temperatures, and unless the temperature is going dangerously high, these procedures may be omitted, if the interne is present to assume responsibility for it.

2. For very high temperatures 107 or more all coverings should be taken off immediately and the child given a tepid sponge. Aspirin gr 10 should be given by mouth unless the patient is vomiting or is unconscious in which case give a double dose 15-20 gr by rectum. Take the temperature every ten or fifteen minutes. If it continues to go up the child may be placed in a tub of water at 100°, the water then being gradually cooled. Sedatives and stimulants should be given as indicated.

Note. These very high temperatures seldom occur, and when they do usually they respond readily to the above treatment. They are not so terrifying as they look! Routine orders usually written on the chart.

Vaccine given at 12 P M. Take the temperature stat. and q 1 hr until it returns to 99.6 (q $\frac{1}{2}$ hr when above 104 on the way up).

Extra blankets and hot water bottles stat.

Codeine gr $\frac{1}{2}$ (h. in thigh) at 12-20 and repeat after hrs. 3 if necessary.

Limit fluids to small sips of water lemon or orange juice.

Aspirin gr 5 and ice-cap to head for temperature over 106.

Daily urine to laboratory during treatment.

Do not be afraid of high temperatures—they are necessary to cure the chorea.

Do not be afraid of large doses of vaccine.

Care of the patient during convalescence

1. Children are kept in bed at least one week after completion of fever therapy—longer if the chorea has been severe or if there has been any evidence of active carditis.

2 High caloric diet to make up for the loss in weight which usually occurs during treatment

3 Occupational therapy (basket weaving, coarse sewing, etc)

4 Transfusion if indicated for anemia

5 Children are sent to a convalescent home from the hospital if possible
Treatment of subsequent attacks by TTV

There is apparently no increased sensitivity to the vaccine. In general we have found that *more* vaccine is required to obtain the desired temperature reaction when a child is being treated a second time with vaccine, than was required during the first course of treatment

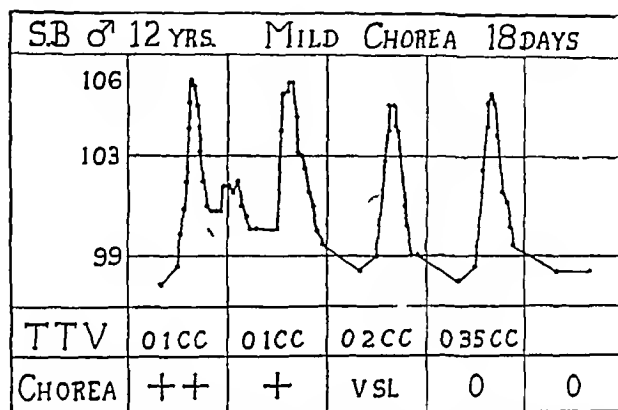


Fig 1—S. B. Mild chorea—first attack. Shows (1) good temperature reactions with small doses of vaccine (2) secondary rise on first day of treatment which occurs in about 50 per cent of the cases (3) good response to short course of treatment

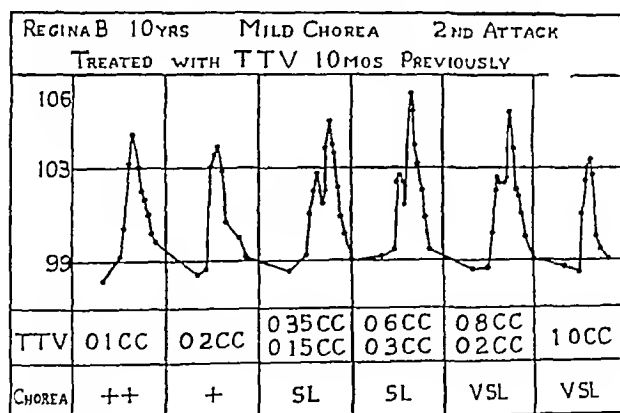


Fig 2—R. B. Mild chorea—second attack. First attack treated with T. T. V. ten months previously. Shows (1) relatively larger doses of vaccine necessary (2) second doses on same day (3) longer course necessary in a second attack

The average number of treatments in the 150 cases reported here was 6.24. In the mild cases the average was 5.14 treatments; in the moderate 6.47 and in the severe cases 8.88. The minimum number of treatments was 3; the maximum 18.

In some children, particularly the severe cases where there has been marked hypotonia, it may be difficult to decide just when the incoordinations are due simply to weakness rather than to chorea. In these cases massage and occupational therapy are given. If the weakness decreases with increased activity, we feel safe in saying the attack is over. If the

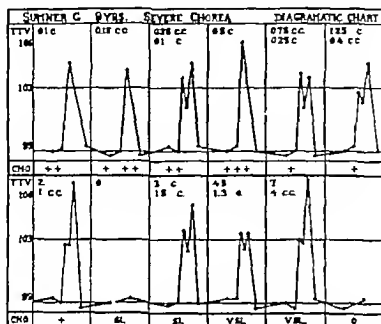
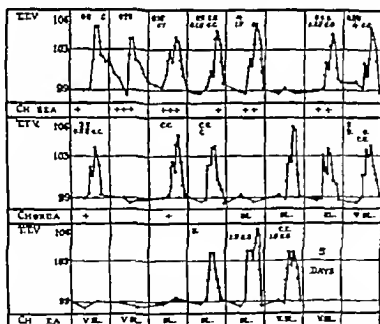


Fig. 3.—G. Severe chorea of two weeks duration. (Case treated at The Nursery and Child's Hospital, courtesy of Dr. Louis Schroeder.) Shows (1) severe chorea responding readily to vigorous treatment (2) good temperature reactions (3) large doses of vaccine necessary



While the majority of cases respond readily to fever therapy, a certain small proportion are disappointing in their results. Fig 4 shows a case of this sort, in which, although the chorea improved from severe to very mild in a reasonable length of time, i.e. ten days, definite choreiform movements persisted for more than two weeks longer. In general

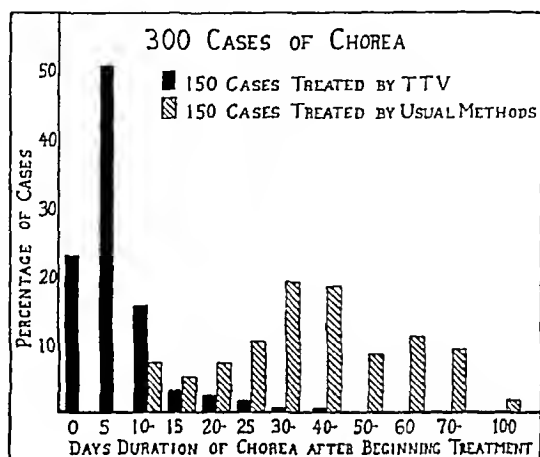


Fig 5—Duration of the chorea after beginning of treatment in 300 cases

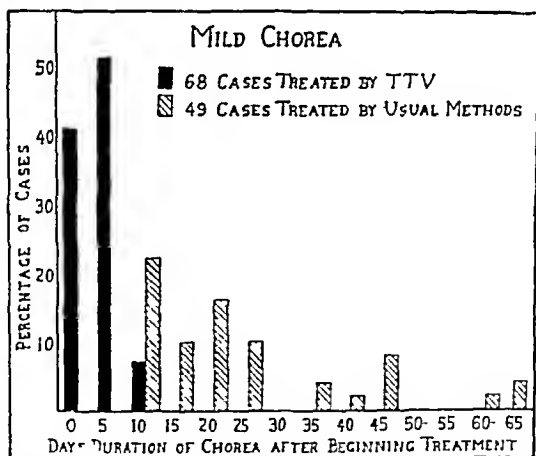


Fig 6—Duration of the chorea after beginning of treatment in 117 mild cases

these difficult cases are likely to be repeaters, or cases in which the duration of the present attack has been long before treatment was begun. While most of these difficult cases fall in the severe group, an occasional one is found in the moderate and even in the mild group. In this latter group it is particularly difficult at times to determine how much if any of the residual movements is due to true chorea, and how much to habit. Of 150 treated cases only 10 per cent responded to

treatment in this way. The longer the course of treatment the more difficult it becomes to obtain adequate febrile reactions, and this fact increases the difficulty in treating some of the more severe cases. In general, the results are prompter and more complete in cases treated early in their first attack.

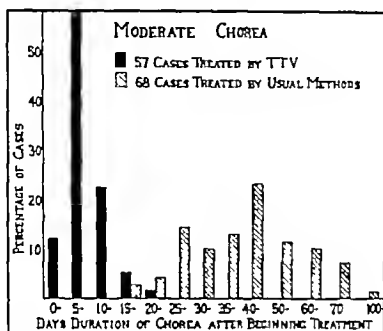


Fig. 7—Duration of the chorea after beginning of treatment in 15 moderate cases.

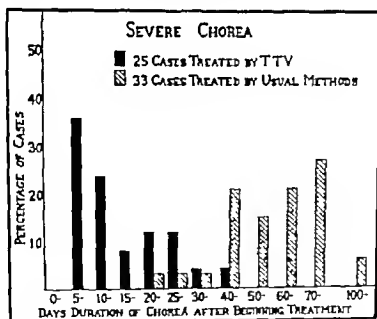


Fig. 8—Duration of the chorea after beginning of treatment in 58 severe cases.

The advantages of the typhoid paratyphoid vaccine method of producing fever are that it is cheap, safe, simple, and produces the desired therapeutic result. The fever follows immediately after the injection, in contrast to the one to two weeks' interval which must elapse before the toxic effects of nirsanol appear.

Because we thought that a temperature maintained at a high level for four or five hours might be more effective than the type of fever obtained

with vaccine alone, and thus necessitate fewer treatments, we tried using a combination of vaccine plus blanket packs in a number of cases. We found that we could maintain the fever for several hours, and got temperature curves similar to those obtained by the radiotherm and diathermy methods. However, the children were more exhausted the following day than when vaccine alone was used. A day without treatment was therefore often necessary, and time was lost. We finally discontinued this method because of the following case:

A P., a girl twelve years old, was admitted in her third very severe attack of chorea. We had treated her second attack a year before with a very good result. Treatment was started as usual, and she showed marked improvement. The fourth dose of vaccine was given at 8:30 one morning. Her temperature reached a maximum of 101° , and then dropped until at 3:30 it was 100° by rectum. In other words she had almost no reaction to the vaccine, and it was all over by mid-afternoon. Because of the poor febrile response to the vaccine she was blanketed about 3:30 P. M. Her temperature rose slowly to 102.8° at 6 P. M., and she was in good condition. The nurse went back to her fifteen minutes later and found that her temperature was 109.8° and that she was unconscious. The resident and internes immediately took measures to reduce the fever and it came down to 101° within three hours. At 11:30 P. M. she began to have convulsions which lasted several hours, the temperature rose to 103° the next morning and she died in the afternoon. Autopsy showed massive lobular pneumonia of both lungs, early vegetative endocarditis of the mitral valve, which had not been sufficient to produce physical signs, and microscopic evidence of past inflammation of the aortic valve. Whether the pneumonia had been caused by the means taken to reduce the temperature we cannot say, it was not suspected before the child was put in the pack.

Study of the brain by Dr. Lewis Stevenson showed:

"A longitudinal section through basal ganglia shows very many distended blood vessels. In the lenticular nucleus and caudate nucleus there are also very many distended blood vessels and to some extent in the posterolateral part of the optic thalamus. Apparently, this is true of the optic radiations as well. There is apparently a slight amount of hemorrhage in the posterior horn of the lateral ventricle, staining the ependyma. In the left hemisphere these distended vessels appear in the internal and external capsules and again in the optic radiation and to some extent in the optic thalamus near the internal capsule.

"Microscopic Examination of Brain—Microscopic sections of caudate nucleus, lenticular nucleus show a mild degree of encephalitis evidenced by small round celled infiltration about some of the smaller vessels. Section of different parts of cortex failed to show this reaction, there is no evidence of meningitis."

This case demonstrated entirely too well what we already knew, namely, that the temperature can rise very high and very rapidly from the use of packs, which cause fever by preventing loss of body heat by radiation. It is important to realize that this fatality was not caused by the vaccine. This is the only death in our series of treated cases.

On the other hand two other children whose temperatures went over 109° from the packs sustained no ill effect, and the beneficial effect on the chorea was definite. The highest temperature from vaccine alone was 108° and this occurred in only one case.

RESULTS

The results with fever therapy in chorea seem to us rather striking. We have made no attempt to run a control series, since this would involve subdivision of cases into groups according to age, sex, number of attacks, duration and severity of attack, and season of the year. This would necessitate a very large number of cases. Moreover, it has been known ever since Sydenham first described chorea that the duration is prolonged, that the average attack lasts six to ten weeks, and that even a mild case may last for months.

For comparison with our results, however, we have gone back over the records of children with chorea treated in Bellevue between 1920 and 1930. We found 150 records with sufficiently detailed and frequent progress notes to determine the actual duration of the chorea in the

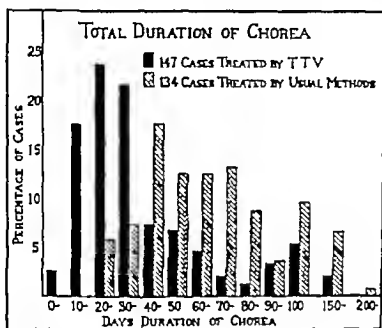


Fig. 9.—Total duration of the chorea in 281 cases. This includes, in the treated group duration before admission plus observation period plus duration of movements after beginning of treatment. In the untreated group duration before admission plus duration in the hospital.

hospital. The treatment given these children included Fowler's solution, sodium salicylate, calcium lactate, thyroid extract, high caloric diet, starvation, hot and cold packs, hydrotherapy, antoserum therapy, rest, catharsis, bromides, luminal, and other sedatives.

The cases in both the comparative and the treated series have been grouped as mild, moderate, and severe. In the comparative group there are a number of children who were admitted as mild cases which became moderate, and others admitted as moderate which became severe. These were put into the moderate and severe groups respectively.

The mild group consists of cases of undemable chorea, but with little functional incapacity. The moderate group includes the cases with continuous, incoördinate movements, with some speech impairment. Such children have difficulty in performing voluntary acts, and the gait

is that of a drunken person, they can run better than they can walk. The severe group is composed of those with marked hypotonia, and pseudoparesis. The hypotonia may be so great as to mask the choreiform movements. These children are unable to speak intelligibly, have difficulty in chewing and in swallowing even liquid food. They have no control whatever over their movements or emotions, and may be unable to try to perform voluntary acts.

The duration of the chorea in the hospital in the group used for comparison, and the duration in days after beginning of fever treatment is shown in Table I.

TABLE I

TYPE	NUMBER OF CASES	AVERAGE DURATION IN DAYS	RANGE IN DAYS
MILD			
Comparative group	48	27.4	10-67
Treated group	68	5.72	2-14
MODERATE			
Comparative group	68	44	15-120
Treated group	57	8.56	3-22
SEVERE			
Comparative group	33	62.4	24-180
Treated group	25	15.8	5-47
WHOLE SERIES			
Comparative group	150	42.6	10-180
Treated group	150	8.5	2-47

A comparison of the two groups confirms the impression that the cases of chorea at Bellevue treated by means other than fever had a considerably longer duration than those treated by induced fever. Figs. 5 to 9 show this graphically.

The question arises whether a somewhat heroic treatment is justified in a disease which in itself is rarely fatal. We feel that it is for the following reasons. It reduces the time spent in the hospital and hence cuts down the expense to the institution. It lessens the period of time lost from school by the child. Although considerable nursing care is required during the treatment period, the nurses are relieved of the prolonged care of an untreated case. The mental agony endured by a person with chorea seems to be great. Several older children who have been treated in well-advanced attacks have come back to us saying that they felt an attack coming, even before we ourselves could have been sure of the diagnosis, and would we "please give them the needles right away" so they could get back to school and not have a bad attack. A sixteen-year-old boy who had had two prolonged attacks was recently treated in his third attack on the adult service at Bellevue Hospital. When asked what he would do if he got a fourth attack, his reply was, "I'd come back for more needles." This is the reaction of those who have had treated and untreated attacks, and seems to us justification for the treatment.

Of the 150 patients with treated attacks reported here 28 patients already had organic rheumatic heart disease. None of these children were harmed in any way by the treatment. Eight children who had definite evidence of active carditis at the time treatment was started, had lost the signs of activity by the time the treatment of the chorea was over. We feel therefore, that the presence of either active or inactive heart disease is not necessarily a contraindication to treatment. We would hesitate to give the treatment in the presence of a very severe carditis as evidenced by a pericardial friction rub but fortunately this combination seldom occurs.

It has been gratifying to hear from physicians in various parts of the country that this method of treating chorea has been used satisfactorily in about 100 other cases. We suspect that those who failed to get good results have probably not followed our technique, and have therefore not obtained good febrile reactions.

A chorea clinic has been established to follow these cases, and we intend to observe them for a period of at least five years from the time of treatment. There seems to be no rational basis for anticipating a reduction in the number of recurrences of chorea in these treated cases. However this question of recurrences as well as that of development of heart disease is being carefully watched and at the end of the observation period data on both treated and untreated cases will be available. So far we have had about 98 per cent follow up of cases. The number of recurrences is relatively small, but since the treatment has been in use only about two and one half years, and since chorea may recur after a lapse of a number of years, our present figures on recurrences have no final value.

Investigators are working continually to perfect methods of producing fever and will doubtless some day devise an apparatus which will be safe in ordinary hands and will lack the unpleasant features of foreign protein shock or of radiotherapy and diathermy and which will at the same time be neither expensive nor elaborate. Until then intravenous injections of typhoid paratyphoid vaccine can be used as a fairly reliable and safe method of treating chorea.

SUMMARY

Intravenous injections of typhoid paratyphoid vaccine as a means of inducing fever have been used in 150 attacks of chorea. Comparison of the duration of chorea in the hospital in 150 attacks treated by other methods show that the duration of the attacks has been reduced from an average of 27.4 days in the mild untreated cases to 5.72 in the mild treated cases from 44 days in the untreated moderate cases to 8.56 in the moderate treated cases and from 62.4 days in the severe

untreated cases to 15.8 days in the severe treated cases. We conclude, therefore, that fever therapy is a satisfactory method of treatment of chorea.

We wish to express our great appreciation to Dr. Charles Hendee Smith for his interest in this study and his very helpful encouragement.

REFERENCES

- 1 Sutton, L. P. *J. A. M. A.* 97: 299, 1931.
- 2 von Kern, Tibor. *Wein klin Wchnschr.* 36: 164, 1923.
- 3 Somogyi, I. *Orvos hetil.* 71: 547, 1927.
- 4 Roeder, F. *Therap. Monatschr.* 33: 54, 1919.
- 5 Pilcher, J. D., and Gerstenberger, H. J. *Am. J. Dis. Child.* 40: 123, 1930.
- 6 Dennett, R. H., and Wetchler, S. *J. Pediatrics* 1: 203, 1932.
- 7 Mas de Ayala, I. *Semana med.* 1: 857, 1930.
- 8 Idem. *Ann. de Fac. de med. Montevideo*, 15 July, 1930.

THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN WITH ANTIPNEUMOCOCCUS SERUM

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ANTIPNEUMOCOCCUS serum has been used extensively in the treatment of pneumonia in adults. For some types the results have definitely proved its value in reducing the mortality rate. The purpose of this paper is to report the results of antipneumococcus serum therapy in the pneumonias of infants and children for similar types of pneumococci and for the more recently isolated types so frequently found in infants and children.

Lobar pneumonia in children (two to twelve years) is notably a benign disease. Under two years, it approaches in severity the pneumonia of adults. Bronchopneumonia is distinctly a very serious disease both in its course and in its mortality rate. For the past three years on the Children's Medical Service at Bellevue Hospital, the mortality rate of bronchopneumonia is approximately 60 per cent and of lobar pneumonia in infants under two years approximately 20 per cent. These figures refer to pneumonias irrespective of etiologic agent. These percentages contrast sharply with a mortality rate of 5 per cent for lobar pneumonia in children over two for the same period of time on the same wards. On the other hand, the mortality rate of pneumonia in adults varies from approximately 20 per cent to 45 per cent, depending upon the type of infecting organism. Obviously other criteria than those used for adults must be employed in the evaluation of antipneumococcus serum therapy in infants and children. The criteria here used are the effect on the severity and progress of the disease as judged by the duration of the pneumonia and the effect on complications.

This study was begun in January, 1932, and included a clinical and bacteriologic observation of 368 patients with all types of pneumonia. This report comprises 207 patients; the remaining 161 are not included as they represent patients having pneumonia due to bacteria other than the pneumococci types for which we have specific serums. During this investigation therapeutic serum was available for the following types of pneumococci: I, II, IV, V, VI, A and B, VII, XIV, XVIII, XIX, and XXII. New serums have been produced for other types since the beginning of this study.

From the Department of Pediatrics, New York University Medical School, and the Children's Medical Service, Bellevue Hospital, and the Research Laboratory of the Department of Health, New York City.

This investigation was made possible by a grant from the Commonwealth Fund to the New York University for research in pneumonia. It has been conducted at the suggestion of and under the direction of Dr. William H. Park. Thanks are also due to Dr. Charles Hendon Smith, director of the Children's Medical Service, Bellevue Hospital, for his criticisms and advice. The bacteriologic typing was done under the supervision of Miss Julia Vinograd. Assistance was also given during the first year by the Altman Foundation.

four hours was from 6 to 9 cc for an infant and from 15 to 25 cc for a child. One dose was usually given after the temperature had remained below 100° F for a period of from two to four hours. Frequently, three or four doses were sufficient and never were more than seven given. Intravenous administration of serum is so much more effective than the intramuscular method that the first one or two doses should be given intravenously, after this first dosage, serum may be given intramuscularly with good results.

Serum Reactions—The amount of serum administered is usually too small to give serum sickness. Only one patient of the 82 treated developed this reaction. One six-month-old baby, having a negative ophthalmic and skin test, died immediately (three to five minutes) after the intravenous injection of 2 cc of antipneumococcus serum. There were no urticarial wheals, however, the death appeared to be associated with serum therapy. Unfortunately, an autopsy was not granted. The delayed reaction following serum therapy was seen rather frequently in varying degrees of severity. From thirty to sixty minutes after intravenous injection of serum a chill, occasionally slight cyanosis, dyspnea, and a thermal reaction, usually amounting to a rise of 2° F, have been observed. This type of reaction is constantly becoming less frequent with the increased refinement of serum. No such reactions occurred following intramuscular injection of serum.

RESULTS

The distribution of the cases studied according to age group is given in Table I. Only 2 of the 36 patients with bronchopneumonia reported were over two years of age.

The group of infants treated with serum is smaller than the children's group because infants commonly have pneumonia due to pneumococci for which we have no therapeutic serum. Table II illustrates that 47 per cent of the 116 infants had lobar pneumonia due to an organism for which we have no specific serum, as compared to 32 per cent of the 278 children with lobar pneumonia.

The predominant infecting organism in the lobar pneumonia of children is pneumococcus Type I, occurring in 32.5 per cent of all children's lobar pneumonia and in 47 per cent of the total 109 children in the *treatable group*. For infants, the predominant pneumococcus in the treatable cases of lobar pneumonia is Type XIV, representing 27 per cent of all infants' pneumonia and 33.6 per cent of the 116 treatable group. In infants with bronchopneumonia, pneumococcus Type XIX occurred rather commonly and had a high mortality rate. This organism was frequently associated with streptococcus or hemolytic staphylococcus (5 of the total 11 patients, all of the 5 died). The significance of pneumococcus Type XIX as the etiologic agent of the disease in such instances was difficult to determine. Three postmortem lung puncture cultures in these 5 patients had no pneumococci. The pre-

TABLE I

DISTRIBUTION OF TYPES OF PNEUMOCOCCI IN SERUM AND CONTROL GROUP OF CASES

TYPE	AGE YEARS	TREATED				UNTREATED				TOTAL
		LOBAR PNEUMONIA		BRONCHO-PNEUMONIA		LOBAR PNEUMONIA		BRONCHO-PNEUMONIA		
		TOTAL	DEATHS	TOTAL	DEATHS	TOTAL	DEATHS	TOTAL	DEATHS	
I	2 12	22	-			30	1			52
	under 2	-	-			3*	2			3
II	2 12	4	-			4	-			8
	under 2	-	-			-	-			0
IV	2-12	1	-			2	-			3
	under 2	-	-			-	-			0
V	2 12	3	-			3	-			6
	under 2	-	-			2	-			2
VI	2 12	5	-	-	-	10	-	1	1	10
	under 2	5	1†	1	1	6†	3†	3	3	15
VII	2 12	1	-	-	-	3	-			4
	under 2	4	1‡	-	-	3	-			7
XIV	2 12	8	-	1	-	1	-	-	-	21
	under 2	17	2	3	2	22	2	5	3	47
XV	2 12			-	-			-	-	0
	under 2			1	-			-	-	1
XVIII	2 12			-	-			-	-	0
	under 2			2	2			1	1	3
XIX	2 12			-	-			-	-	0
	under 2			2	1			0	3	11
XXII	2 12			-	-			-	-	0
	under 2			2	-			-	-	2
Mixed types VI III, XIX	under 2					1	-			1
VI	under 2							1	-	1
XVII	under 2							1	-	1
VI, VII	under 2							1	1	1
XIV	under 2							1	-	1
XIX, XI	under 2							1	-	1

Excluded from study because no infants were treated with Type I serum.

†Excluded from mortality table because case of meningitis complicating pneumonia when treated.

‡Excluded from mortality table as meningitis complicating pneumonia when treated—two such cases.

§Excluded from mortality group died of *Staphylococcus aureus* lung abscesses and empyema—autopsy

TABLE II

INCIDENCE OF LOBAR PNEUMONIA IN INFANTS AND CHILDREN

(Bellevue Hospital January 1932—July 1933)

AGE (YEARS)	NO. OF CASES			
	UNTREATED		TREATED	TOTAL
	NO SERUM AVAILABLE	SERUM AVAILABLE (CONTROL GROUP)		
under 2	54	86*	26†	116
2 12	51	65	44	160
Total	105	101	70	276

Including one case of meningitis.

†Including two cases of meningitis and three Type I pneumococcus in infants.

dominance of Type XIX might also be due to seasonal variation, there were more pneumococcus Type XIX infections both in patients with upper respiratory infection and with pneumonia in 1932-1933 than in the winter of 1932. Pneumococcus Type VI occurred frequently in infants in both lobar pneumonia and bronchopneumonia.

The mortality rate for both bronchopneumonia and lobar pneumonia is shown in Table III.

TABLE III
MORTALITY RATE IN TREATED AND CONTROL GROUP

	BRONCHO PNEUMONIA		LOBAR PNEUMONIA		LOBAR PNEUMONIA AND BRONCHO PNEUMONIA		MORTALITY PER CENT
	TOTAL	DEATHS	TOTAL	DEATHS	TOTAL	DEATHS	
Cases treated	12	6	69*	2	81	5	9.8
Cases untreated	24	17	96†	3	120	20	16.6

*Excluding one case of pneumococcus meningitis complicating pneumonia when treated.

†Excluding two cases of pneumococcus meningitis associated with pneumonia and three infants with Type I lobar pneumonia.

Although the percentage of mortality for the treated cases is lower than that for the control group, the entire series is too small to warrant a definite conclusion as to the efficacy of serum in reducing the mortality rate.

The bronchopneumonia group is small, not because of the infrequency of the disease, but because we are more often unable to obtain pneumococci from repeated laryngeal swabs. Of the 90 patients with bronchopneumonia studied, only 50 had pneumococci in the cultures from laryngeal swabs. Of these 50, 26 died and cultures of post-mortem lung punctures made immediately after death on 7 showed hemolytic staphylococci or streptococci, but no pneumococci could be isolated, from 9 patients pneumococci were cultured from postmortem lung punctures. No postmortem lung puncture was done on 9 of the 26 patients, and 1 puncture was sterile.

An objective criterion for the efficacy of antipneumococcus serum in lobar pneumonia is shortening the duration of the disease. A crisis usually occurred from twelve to twenty-four hours following the introduction of serum therapy, frequently after the administration of only 7 to 10 cc in twelve hours' time. In infants, this period is prolonged from twenty-four to forty-eight hours. The crisis was judged by fall in pulse rate and respiratory rate, and other evidences of loss of toxicity.

Charts 1, 2, and 3 show the effect of serum on the duration of the disease. The day of crisis of all patients with lobar pneumonia due to pneumococci for which we have therapeutic serum is given in Chart 1. A crisis was observed by the fifth day of the disease in 60 per cent of the

49 patients treated with serum as compared to 20 per cent of the 79 patients in the control group. Many of the serum treated patients had a crisis before the fifth day of the disease.

The most consistently satisfactory results have been obtained with pneumococcus Types I and XIV serums. Chart 2 illustrates the day

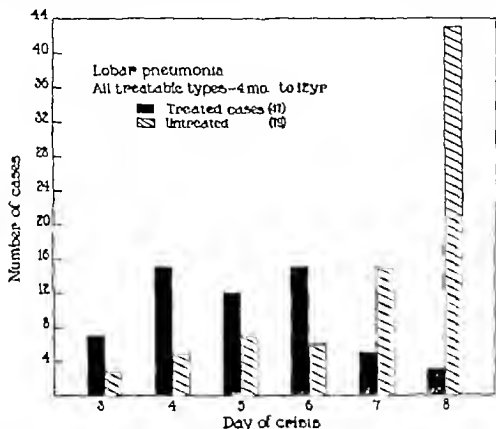


Chart 1.—Duration of disease in all patients receiving serum compared with a control untreated group. Greater number of treated cases show early crisis.

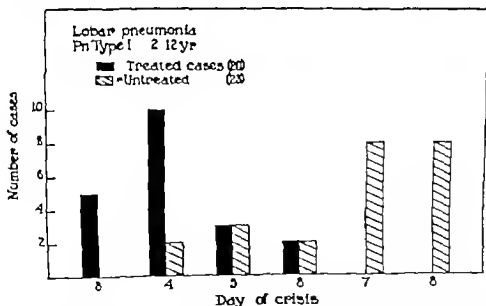


Chart 2.—Duration of Type I pneumococcus pneumonia among treated children compared with untreated control group. The course of the disease is definitely shorter in the treated group. Seventy five per cent of the treated patients had a crisis before the fifth day as compared with 10 per cent for the control group.

of crisis of patients with pneumococcus Type I pneumonia in children. It can be seen at a glance that serum definitely shortens the disease, a crisis as early as the third day in 5 of the 20 treated cases is noted,

whereas not a single patient of the 25 untreated cases had such an early crisis. The duration of the disease was never longer than six days in any patient receiving serum (Type I), while in 16 of the 23 control group a crisis occurred after the sixth day. In short, 75 per cent of the treated patients had a crisis before the fifth day as compared to 10 per cent for the control group. Antipneumococcus Type XIV serum has been similarly effective in shortening the disease in both infants and children as shown in Chart 3. The duration of lobar pneumonia in infants on the average is several days longer than in children. None of the 18 patients receiving serum had a crisis later than the seventh day, while the duration of the disease in 18 of the 27 untreated patients was longer than seven days. In other words, a crisis was observed in 80 per cent of the 18 patients before the seventh day as contrasted with 19 per cent (5 of the 27) of the control group.

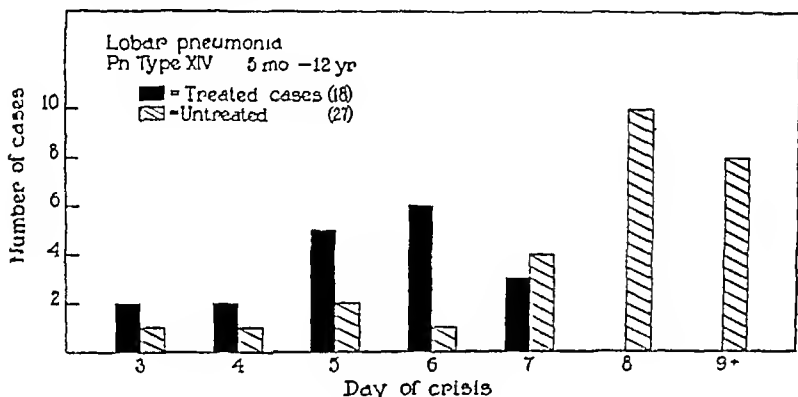


Chart 3—Duration of Type XIV pneumococcus pneumonia of control and treated group for all ages. The treated patients had later crises eighth and ninth days; no similar case in the treated group. The disease is shorter in the treated patients.

Although Chart 1 definitely suggests that serum is efficacious in shortening the disease, all serums are not equally effective. Chart 1 represents largely (80 per cent treated, and 63 per cent untreated) the results with antipneumococcus serums Types I and XIV. On the other hand, the results of antipneumococcus Type VI serum do not seem to have been so decisive. An analysis of 21 patients, 7 treated and 14 untreated, reveals no appreciable difference in the two groups. In fact, 2 untreated patients had a crisis as early as the third day, whereas the earliest for the treated group was the fourth day. A probable explanation for these observations aside from the possible inefficacy of antipneumococcus Type VI serum is the difficulty of diagnosis. Since pneumococcus Type VI A and B is a frequent inhabitant of the throats of infants and children, errors in diagnosis with this organism may be easily made.

The medical histories were taken with great care to determine the exact day of onset of the pneumonia, nevertheless, there was a small

number in each group in which the duration of the disease was indefinite due to inability to date the onset or to date the crisis, as for example, in the development of an empyema

On the whole, the serum treated group showed signs of greater toxicity before treatment than the nontreated group. This observation is in part indicated by the fact that there was a greater number of two lobe pneumonias in the serum group, 13 of the 69 (18 per cent) treated patients had two or more lobes involved, whereas only 8 of the 94 (8 per cent) control group had pneumonic consolidation of more than one lobe

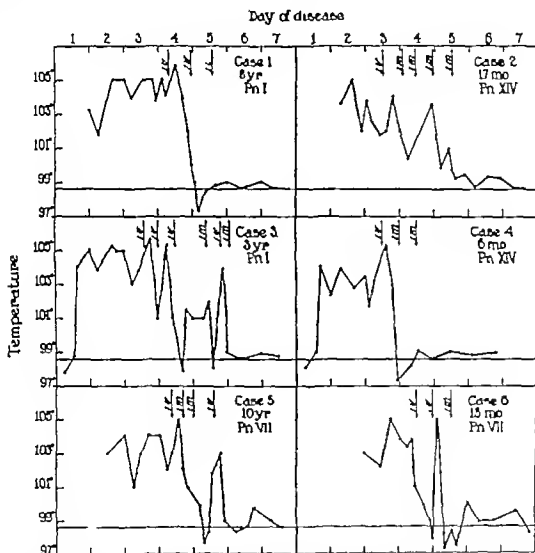


Chart 4—Temperature curves of selected patients, showing usual response to anti pneumococcus serum in lobar pneumonia. The arrow represents serum administration of Types I, XIV and VII antipneumococcus serum, intravenously (i.v.) or intramuscularly (i.m.) Cases 1 and 4 indicate a common type of response. The latter developed lobar pneumonia in the hospital. Case 3 also developed lobar pneumonia in the hospital and illustrates the result of inadequate treatment. A second dose of serum should have been given on the fourth day of the disease. Small quantities of serum were used in Cases 1, 4, 5 and 6.

The response to the administration of serum can best be seen by reference to the temperature charts of a few selected cases showing typical response (Chart 4). Pneumococcus Type I is the predominant type for children and Type XIV for infants in this series. The thermal reaction following intravenous injection is also shown, particularly in Case 3 where a certain lot of serum having a high content of chill producing

fraction was used. The loss of toxicity following serum administration is as impressive as the drop in temperature and is correlated with it, sometimes antedating the final temperature fall to normal. Case 2 illustrates the use of intramuscular serum injections after an initial intravenous dose.

Patients with bronchopneumonia show a different response to serum treatment. A crisis is not usually observed as in the lobar pneumonia group, and hence a fall in temperature cannot usually be used as a criterion for the efficacy of serum. We treat bronchopneumonia patients for only forty-eight hours, using the dosage of from 500-1000 units per pound of body weight for a twenty-four-hour period (or 10-15 cc. in 3-4 doses per day). Chart 5 represents the temperature curves

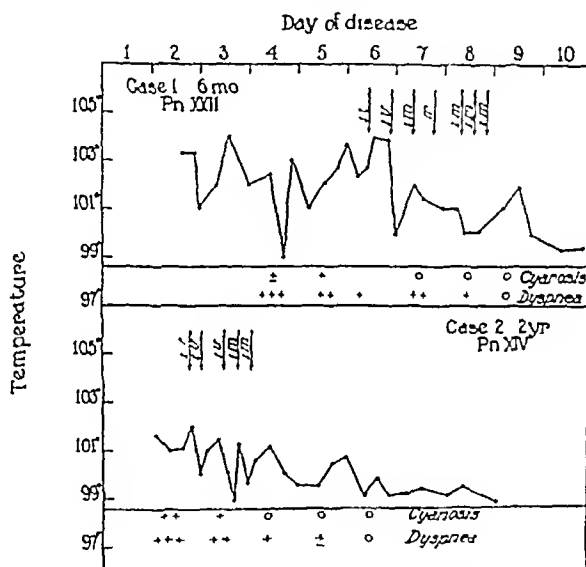


Chart 5.—The temperature curve of two patients with bronchopneumonia receiving antipneumococcus serum Types XII and XIV. Temperature response is not like that in lobar pneumonia. (See Chart 4). Improvement is clinical as indicated below in decreasing cyanosis and dyspnea. More frequent and larger dosages of serum are necessary in bronchopneumonia.

of patients with bronchopneumonia who received serum. Both patients were very sick, with cyanosis and marked dyspnea. These symptoms were practically lost after forty-eight hours of treatment and were diminished after only twenty-four hours. There is no crisis, however, and a comparison of these temperature curves with those in Chart 4 reveals this fact.

A study of the duration of the disease with reference to the period of hospitalization is shown in Chart 6. It becomes apparent that admission to the hospital early in the disease does not in itself act to shorten appreciably the duration of Type I pneumococcus pneumonia in the same age group. To illustrate, 13 patients admitted to the hospital

on the second day of the disease received serum. All of these patients had a crisis by the end of the fifth day and most of them before. The 9 patients who had equal hospital care but no serum admitted on the second day of the disease, continued to run a long course with the crisis on the sixth to ninth day. Although the serum treated group has a greater number of patients with early hospital admissions, Chart 7 clearly indicates that this factor in itself does not tend to shorten the disease.

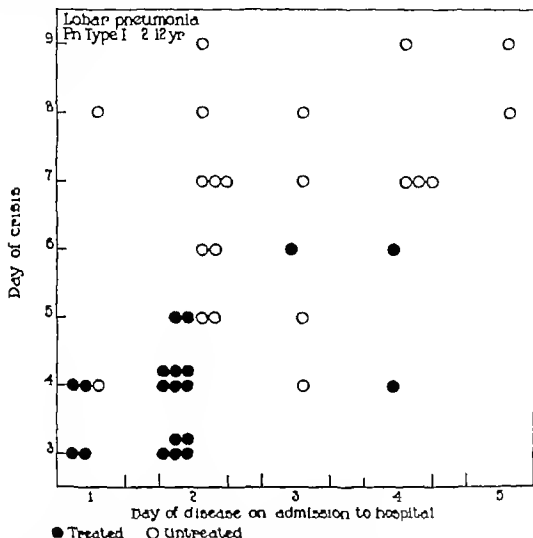


Chart 6—Duration of the disease in treated and control groups with reference to period of hospitalization in pneumococcus Type I pneumonia. Each untreated patient is represented by an open circle each treated patient, by a black circle. Although more serum treated patients were admitted to the hospital early in the disease this factor alone does not shorten the disease. Patients untreated admitted on the same day of illness have a longer course.

Finally, only one patient of the 69 cases of lobar pneumonia treated with serum developed empyema. This seven year-old child had 2 doses of pneumococcus Type V serum a total of 10 c.c. 15,000 units on the fifth day of the disease and a crisis ensued. The empyema Type V was demonstrated after an afebrile period of three weeks. Of the 94 cases in the control group 4 developed empyema, two of the pneumococcus Type I origin, one pneumococcus Type XIV, and one Type V. A spread of the pneumonia to a new lobe was observed in 2 patients in the control group. There was no such complication in the treated group. No

patient receiving serum developed meningitis. Pneumococcus meningitis Type XIV was diagnosed in one patient in the control group, 3 infants had pneumococcus meningitis Type VI, all of whom died. One of these 3 infants received intravenous and intrathecal antipneumococcus serum. All 3 of these infants are excluded from the mortality rate.

The above facts tend to indicate that the complications following lobar pneumonia may be decreased by administration of antipneumococcus serum. Perhaps this difference is in part due to the fact that all the

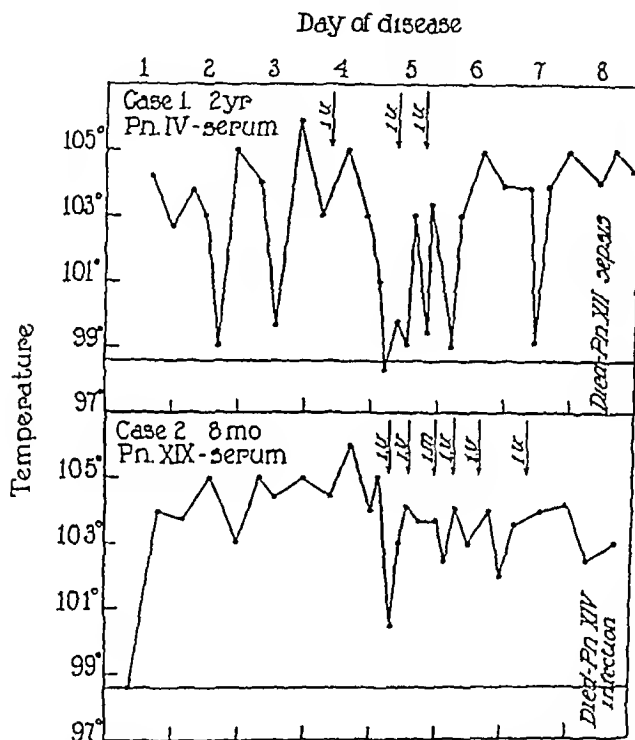


Chart 7—Temperature curves of two patients failing to respond to serum. Case 1 is that of a two-year-old boy having Types IV and XII pneumococci in the laryngeal swabs. Serum for Type IV was given (no therapeutic serum for Type XII). Blood culture taken before treatment was positive for pneumococcus Type XII. Patient died with pneumococcus type XII sepsis and meningitis. Case 2 was treated with antipneumococcus Type XIX, the type obtained from 2 laryngeal swab cultures. No response to treatment. Pneumococcus Type XIV empyema developed. Probably an error in diagnosis of the etiologic agent was made. Pneumococcus Type XIX is most likely a nonpathogenic inhabitant of the throat.

serum treated group received serum relatively early in the course of their disease. It seems significant that the one case that developed empyema following serum therapy, received treatment late in the disease.

That pneumococci may be found in the throat of a normal person is a well known fact. It becomes difficult at times to evaluate the presence of pneumococci in cultures from laryngeal swabs, as is illustrated in Case 2, Chart 7. Pneumococcus Type XIX was cultured from two laryngeal swabs and from the pus from the ear of a baby with lobar

pneumonia (confirmed at autopsy) Antipneumococcus serum Type XIX produced no appreciable improvement in the patient's condition. A pneumococcus Type XIV empyema, septicemia, and meningitis ensued, with subsequent death. In this patient, it seems reasonable to assert that the death was not due to failure of antipneumococcus serum but rather to a failure in the diagnosis of the etiologic agent.

Multiple pneumococcus infections are confusing also, but fortunately were infrequently found in the group reported. It was more commonly found in the group for which we have no serum. Case 1 (Chart 7) is that of a child having both Types IV and XII pneumococci in equal proportion in the culture from the laryngeal swab. A blood culture was taken before the administration of antipneumococcus serum Type IV. Therapeutic serum for Type XII was not available. The following day a report of the blood culture revealed only pneumococcus Type XII, a fatal meningitis developed and pneumococcus Type XII was cultured from the spinal fluid. Repeated laryngeal swabs revealed only Type XII pneumococcus.

Cultures of lung suction punctures might help in determining the true etiologic agent of the disease in such cases as the 2 cited above and also in patients with bronchopneumonia where the pneumococci, even when found frequently, may not be the true or sole etiologic agents of the disease. Pneumococci isolated from patients with bronchopneumonia are often associated with hemolytic streptococci or hemolytic staphylococci. On postmortem lung puncture cultures of patients with such mixed bacteriology, hemolytic staphylococci or hemolytic streptococci are usually found without pneumococci. Autopsy in many of these patients disclosed multiple abscesses in the lungs. Hence, it is suggested that even though pneumococci are found in the cultures from the laryngeal swabs of babies with bronchopneumonia these organisms in many instances are probably not the etiologic agents of the disease. Blood cultures and cultures of other body fluids on a number of babies have been positive for streptococci even though pneumococci have been cultured from the swabs.

Although the laryngeal swab method of culture does lead to errors as indicated, on the whole it is a more feasible method than lung suction puncture and is satisfactory for the lobar pneumonia group in a very high percentage of cases.

Perhaps the more striking results of antipneumococcus Type I serum therapy is partly attributable to a greater accuracy in diagnosis of the type of infecting organism in patients with pneumococcus Type I pneumonia. During this investigation a moderate number of children and infants with acute pharyngitis and acute bronchitis were studied bacteriologically. Pneumococcus Type I was found only once in these cultures, whereas other types of pneumococcus were isolated rather com-

HISTORY OF PREVIOUS PREGNANCIES

Twenty-nine of the mothers comprising this group were primiparas. Thirty-eight mothers gave a history of having had a total of 68 abortions. Eleven mothers had a total of 18 stillborn infants, and 12 others had previously borne 19 live premature infants. Six of these mothers had both abortions and stillbirths, or both abortions and previous prematures. Twenty-three mothers had had full-term infants, with the premature infants noted here as their first early termination of pregnancy.

TREATMENT OF MOTHERS

In general the parents dealt with have been careless about their own treatment. Only 13 of the 97 mothers are known to have received antenatal treatment and none of these received a sufficient amount as measured by present standards. Most mothers who went to prenatal clinics, visited them late in pregnancy or immediately before delivery. Three of the infants born of this group of treated mothers died shortly after birth. In one of these infants, evidence of syphilis was found at autopsy.

TABLE III
SYMPTOMS*

Snuffles	26
Enlarged liver	11
Enlarged spleen	7
Desquamation	16
Indurated shiny palms and soles	10
Fissures	9
Rash	7
Mucous patches	1
Hemorrhage	9
Edema	4
General appearance	3
Adenopathy	2
Failure to gain	4

*The limited number of some of the manifestations recorded is in large part due to the fact that treatment was started immediately upon the report of positive serologic findings in one or both parents, even though the infants showed no signs of disease.

SYMPTOMS

Forty-eight infants did not have recognizable clinical signs of syphilis at any time. The symptoms noted in the remaining 70 are listed in Table III. Snuffles was the most frequently noted symptom, occurring in 26 infants. In 6 of these the discharge was bloody. One of these infants had a saddle nose deformity at birth. The usual time of appearance of snuffles was between the third and the fourteenth day. Characteristic desquamation involving the palms and soles, and the face usually associated with other signs of syphilis, occurred in 15 infants. An enlarged liver was found in 11 babies, 7 of whom also had an enlarged spleen. Bleeding fissures about the nose, mouth or anus occurred in 9 infants. Edema was present in 4 infants involving par-

ticularly the lower limbs, abdomen, and scalp. An eruption was recorded in 10 cases, in 9 of which it was maculopapular in type, in the other one mucous patches occurred. Hemorrhage was present in 9 of these infants accompanying unmistakable clinical signs of syphilis. The bleeding came from the rectum in 6 infants, the stomach in one, the vagina in one, and generalized ecchymosis occurred in one other.

RELATIONSHIP OF SYMPTOMS TO EARLY MORTALITY

Thirty two of the premature infants died during their stay in the hospital, as listed in Tables I and II. Nine of these died within twenty four hours after admission, which was usually a few hours after their birth*. Fourteen more died within two weeks, and the remaining 9 died before reaching the age of two months. Twenty-one infants had severe symptoms of syphilis shortly after birth, and of these, 18 died despite treatment. At postmortem, besides syphilitic changes observed, 2 had intracranial hemorrhage, 2 had bronchopneumonia, and 1 pneumococcal meningitis. Five infants who died weighed under one thousand grams. Of the 12 remaining infants, syphilitic changes were found in 5 at post mortem examination. Death was due in 5 instances to intracranial hemorrhage in 2 to atelectasis, and in 2 to bronchopneumonia.

TREATMENT

Antisyphilitic treatment has been started in each infant routinely, upon the discovery of a positive Wassermann reaction in either parent. We feel that immediate treatment is justified for several reasons. First a premature interruption of gestation in a syphilitic mother even though she has been treated during pregnancy is presumptive evidence of syphilis in the infants. Second, the earlier the treatment is instituted the better the prognosis, except in cases of severe visceral syphilis, and third as Wile and Shaw¹³ von Mettenheim¹² and others have observed it is becoming increasingly difficult to make a diagnosis of congenital syphilis early. These observers note that the picture of congenital syphilis has changed due to the treatment of mothers during pregnancy, so that very few of the infants show definite clinical evidence of the disease at birth. If these infants are allowed to go untreated, the disease may manifest itself as late as puberty, or even later.

Some American observers who begin treatment before the manifestation of symptoms are Atlee and Tyson²² who immediately treat all infants who have positive cord Wassermann reactions. McCord²³ also advocates this. Dunham²⁴ treats all offspring of mothers who have had an active or recent syphilitic infection and have not received

Babies born at home or in hospitals other than Michael Reese who need incubator care, are usually transported by special ambulance to the Sarah Morris Premature Station immediately after birth.

treatment antenatally Wile and Shaw¹³ believe that treatment should be instituted for all infants born of mothers with recent syphilis, even though treated during pregnancy Kolmer¹⁴ noted that it was advisable to regard every child of syphilitic parentage as infected, and administer antisyphilitic therapy even though the infant appears healthy and gives a negative Wassermann reaction, especially if either parent is uncured Taylor¹⁵ believes that all children born of syphilitic mothers treated during pregnancy, should be treated prophylactically for at least two years

There are many European observers who believe that treatment should be given at birth to all offspring of syphilitic parents, regardless of the duration of the infection, and also to supplement the prenatal treatment given to the mother Klaffen¹⁶ believes that every descendant from syphilitic parents should be subjected to prophylactic treatment He noted that the mortality of infants with congenital syphilis was around 30 per cent, and that the mortality of those treated immediately was only 9.1 per cent In view of this fact, he undertook preventive treatment in apparently healthy children born of syphilitic parents with a result that the mortality was reduced to 7.9 per cent In another article, the same author¹⁷ states that such authorities as Gallot, Jadassohn, Fischl, Finkelstein, Davidsohn, Pazzke, Pinard, Slavik, Noeggiath, Richter, Erich Muller, and others advocate the preventive treatment in newborn infants of syphilitic parents Hoffman¹⁸ believes that infants born of syphilitic mothers who have had a more or less energetic treatment during pregnancy, should be subjected to preventive therapy He states that one must take exception to the rule, "no treatment without previous diagnosis"

Adams, in discussing a paper by Nabarro¹⁹ stated that the battle in congenital syphilis is over in the first two or three months, and so institutes immediate treatment in all infants, even if their mothers had prenatal therapy Maifan²¹ suspects the presence of congenital syphilis in infants born of infected parents, even when no certain signs of the disease exist, and even when the Wassermann reaction is negative, he would treat the infant as if the disease were certain Pillsbury²² believes that it is hardly logical to regard the almost certainly infected infant of a mother with early syphilis as cured by prenatal treatment He notes that at the Welaender homes, in the Scandinavian countries, where the long-continued observation of syphilitic mothers and children is unparalleled, it is the custom to continue treatment of the infant after birth regardless of the absence of syphilitic symptoms Scherber,²³ von den Steinen,²⁴ and Lereboullet,²⁵ also believe that all offspring of syphilitic parents should be subjected to prophylactic treatment

While these observers are in the majority, there are many authorities who take an opposite stand Boas²⁶ is strongly opposed to treat-

ing any child until the diagnosis is definitely established Buschke and Gumpert³⁷ conclude that a child of syphilitic parents must by no means necessarily be infected, and they are very careful in the selection of children for prophylactic therapy Hahn³⁸ institutes treatment in the offspring of syphilitic parents when their Wassermann reaction is negative only if they fail to gain properly in weight

METHOD OF TREATMENT

Until the past twelve months, the routine treatment, either prophylactic or in the presence of symptoms, was to use mercury in the form of inunctions combined with oral administration of mercury and chalk, together with sulpharsphenamine injected intramuscularly Mercury with chalk was started in the small dosage of one eighth grain daily because of the ease with which it causes diarrhea in very small infants The dose was increased until infants one year old were receiving one grain three times daily Inunctions of five grains of mercury ointment were used only during their stay in the hospital, and were given once daily for seven days, with seven days' rest Sulpharsphenamine, in a dosage of 0.002 gram per kilogram of body weight, was injected once a week for six weeks with six weeks of rest and this course was repeated twice during the first year The mercury with chalk was given during the same time that the arsenical was being administered

STOVARSOL THERAPY

During the past year, stovarsol has been the only drug employed in our clinic Stovarsol acetarsono, or acetylaminohydroxyphenylarsonic acid, known as 'spirocid' in Germany, contains 27.1 to 27.4 per cent arsenic and is a white powder odorless, with a slightly acid taste It is manufactured in the form of 0.1 gram and 0.25 gram tablets The 0.1 gram tablets are the only ones which were used in this study A complete description of this drug is given by Maxwell and Glaser³⁹

The dosage given to infants as reported in the literature varies markedly in amount Thus, Soldin and Lesser⁴⁰ gave doses to infants in increasing amounts as follows

- $\frac{1}{4}$ 0.25 gram tablet once daily for three days
- $\frac{1}{4}$ 0.25 gram tablet twice daily for three days
- $\frac{1}{4}$ 0.25 gram tablet 3 times daily for three days
- $\frac{1}{2}$ 0.25 gram tablet twice daily for three months and from then on
- $\frac{1}{2}$ 0.25 gram tablet 3 or 4 times daily until a minimum total dosage of 35 grams had been administered

Tuscherer⁴¹ working in the University clinic in Berlin, also used large doses both in infants and older children His regimen was to give the following

- $\frac{1}{4}$ 0.25 gram tablet once daily for three days
- $\frac{1}{4}$ 0.25 gram tablet 2 times daily for three days

- $\frac{1}{4}$ 0.25 gram tablet 3 times daily for three days
- $\frac{1}{4}$ 0.25 gram tablet 4 times daily for three days
- $\frac{1}{2}$ 0.25 gram tablet 4 times daily for three days
- 1 0.25 gram tablet 2 times daily for three days
- 1 0.25 gram tablet 3 times daily until a total dosage of 21 grams in forty one days was given. At least one more similar course was repeated, even though the infants had a negative Wassermann reaction at the end of treatment

Klaften gives newborn infants one-half of a 0.25 gram tablet the first day after birth. During the first week he gives three and one-half tablets combined with mercury. The whole course of prophylactic treatment thus instituted lasts eleven or twelve weeks, during which time fifteen grams, or sixty 0.25 gram tablets are administered. In premature infants, however, he gives smaller quantities. One-quarter of a 0.25 gram tablet is given the first day of the first week of treatment, and half a tablet the remaining six days. In the second week, one half tablet twice daily is given, and without further increase a total of four to six grams is administered.

Smaller doses are advocated by some. Oppenheim and Fessler⁴² give a daily dose of 0.01 to 0.03 gram to newborn infants, and to nurslings up to six months 0.05 to 0.12 gram daily. Courtin,⁴³ quoting Danzer, reports that his system is to give a daily dose of 0.01 gram for three months, giving a total dose of only four to five grams of the drug. Kiosl⁴⁴ recommends a dose of 0.02 gram per kilogram of body weight for four consecutive days each week for six or eight weeks. Other observers, Erich Muller,⁴⁵ von den Steinen,³⁴ Wegner,⁴⁶ and Blesehmann⁴⁷ also believe that a rest should be given after several days of treatment to allow the patient to eliminate the arsenic taken.

Scherber³³ gives three 0.1 gram tablets daily and increases the dosage to six tablets daily. He obtains the permissible total dosage by dividing the weight of the child in kilograms by four. Thus, a ten-kilogram infant would receive 2.5 grams in a total course.

Bratusch-Marrain⁴⁸ recommends that the drug be given in relation to the body weight of the infant. He gives the following

- 0.005 gram per kilogram daily for 1st week
- 0.010 gram per kilogram daily for 2nd week
- 0.015 gram per kilogram daily for 3rd week
- 0.02 gram per kilogram daily for 4th week
- and continues at this dosage for five more weeks, after which a rest period of six weeks is instituted

Since extreme care in administering arsenic to young infants is always necessary, it appears that this type of dose is advisable. I have used this system advised by Bratusch-Marrain,⁴⁸ after seeing it used

so successfully by Abt and Traisman⁴⁴ at Northwestern University Clinic. This method has also yielded excellent results when used by Rosenbaum.²⁰

Three such courses are given the first year, and are continued at least one more year. Wassermann tests are made at the end of each rest period.

Thirty-two infants have been treated with stovarsol. Of these, 8 have had this drug alone, 7 have had mercury in combination with stovarsol, and the remaining 17 have had previous courses of mercury and sulpharsphenamine.*

EFFECT OF STOVARSOL ON SYMPTOMS AND ON WASSERMANN REACTIONS

In 9 infants who had snuffles the condition cleared up in from four to eight weeks. Five of these infants received mercury and chalk together with stovarsol, with no more rapid change in symptoms than those on stovarsol alone. Five infants had splenic and hepatic enlargement. In 3 of these the liver and spleen were no longer palpable at the end of one course of therapy, in the other 2 the liver was no longer palpable at the end of two courses, but the spleen was still enlarged. It was however, in each case, smaller than when originally noted, and much less firm in consistency.

Six of the 17 infants who received stovarsol after having previously been treated with mercury and sulpharsphenamine, were under one year of age. All of these infants were clinically and serologically negative when stovarsol treatment was begun. Stovarsol was used simply to complete an adequate amount of therapy.

The blood Wassermann and Kahn reactions have been negative after one course of therapy in all the infants treated with stovarsol, or with mercury and stovarsol, and all have remained so. Twelve infants have had 3 negative reactions when taken at the end of each rest period, and 3 have had two such negative reactions. One infant who had a two plus Wassermann and Kahn reaction following the use of one course of mercury and sulpharsphenamine, had a reversal of the reaction following the added use of one course of stovarsol. The reaction remained negative on two further examinations.

A favorable effect of stovarsol on the Wassermann reaction in infants with syphilis has been reported by all authors. Abt and Traisman⁴⁵ had positive Wassermann reactions reversed after treatment in 14 out of 18 infants. Rosenbaum²⁰ reversed the positive Wassermann reactions in all of 9 children who had treatment begun during their first year. Maxwell and Glaser³⁹ treated 10 infants under one year, 4 of whom had negative Wassermann reactions at the start that remained negative while 6 others with positive Wassermann reactions

Infants are brought to the clinic each week and only enough of the drug to last one week is given. It is advised that the drug be dissolved in water or weak tea and given thirty minutes before a feeding.

- $\frac{1}{4}$ 0.25 gram tablet 3 times daily for three days
- $\frac{1}{4}$ 0.25 gram tablet 4 times daily for three days
- $\frac{1}{2}$ 0.25 gram tablet 4 times daily for three days
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Smaller doses are advocated by some. Oppenheim and Fessler⁴² give a daily dose of 0.01 to 0.03 gram to newborn infants, and to nurslings up to six months 0.05 to 0.12 gram daily. Courtin,⁴³ quoting Danzer, reports that his system is to give a daily dose of 0.01 gram for three months, giving a total dose of only four to five grams of the drug. Krösl⁴⁴ recommends a dose of 0.02 gram per kilogram of body weight for four consecutive days each week for six or eight weeks. Other observers, Erich Muller,⁴⁵ von den Steinen,³⁴ Wegner,⁴⁶ and Bleschmann⁴⁷ also believe that a rest should be given after several days of treatment to allow the patient to eliminate the arsenic taken.

Scherber³³ gives three 0.1 gram tablets daily and increases the dosage to six tablets daily. He obtains the permissible total dosage by dividing the weight of the child in kilograms by four. Thus, a ten-kilogram infant would receive 2.5 grams in a total course.

Bratusch-Marrain⁴⁸ recommends that the drug be given in relation to the body weight of the infant. He gives the following

- 0.005 gram per kilogram daily for 1st week
- 0.010 gram per kilogram daily for 2nd week
- 0.015 gram per kilogram daily for 3rd week
- 0.02 gram per kilogram daily for 4th week
- and continues at this dosage for five more weeks, after which a rest period of six weeks is instituted

Since extreme care in administering arsenic to young infants is always necessary it appears that this type of dose is advisable. I have used this system advised by Bratusch-Marrain,⁴⁸ after seeing it used

cellaneous and unknown, 161 cases. Hnsten⁵⁵ investigated the fate of 39 cases of congenital syphilis and found that one half died of intercurrent infections, with only 16 living at the time of his study. Antoniewicz⁵⁶ reported that 15 of 46 children, or 32.4 per cent, treated after manifest symptoms occurred, died (10 before reaching the age of one year), while in a group of 36 infants born of syphilitic parents and treated prophylactically from birth on, only 6 per cent died, and all of these were over one year of age. Lange⁵⁷ observed 100 syphilitic infants for ten years. Sixty-seven of these died, 52 from respiratory and intestinal diseases. Ten of the infants were premature, and only one survived. He noted that even though symptoms of syphilis had disappeared after treatment, the children withstood infections poorly. White and Veeder⁵⁸ reported the results of treatment of 197 cases, less than two years of age. Sixty died, or a mortality of 30.1 per cent. Fourteen of the infants treated were premature, and 6, or 43 per cent, of them died.

Forty of the 58 infants followed in the clinic have had infections of varying degrees of severity. All of these infants have had one or more attacks of nasopharyngitis and 15 have had otitis media. Bronchopneumonia occurred in 10 infants, bronchitis in 4, cervical adenitis in 3, pyelitis in 1 and gastroenteritis in 6.

Premature infants are naturally more susceptible to secondary infections because of their size and lack of immunity to disease so that the infections that occurred in this group cannot necessarily be blamed on a lowered defense mechanism due to syphilis. The hygienic surroundings of this group of infants at home have been very inferior and it is probable that exposure to respiratory infections in particular has been frequent.

Mild symptoms of rickets occur with frequency in many premature infants even with adequate prophylactic therapy. Four of this group developed moderately severe rickets. Three of these infants were negroes.

One infant in this group had hydrocephalus, and one had spina bifida occulta. Otherwise, no abnormalities have been discovered.

At the present time there are under observation in the premature clinic 38 of these children. Twelve of them are over two years of age, 11 are between one and two years and 15 are under one year. Fifteen others were treated for at least two years, but have since been lost track of. Two others over two years of age are now in institutions. During the time that the infants were under clinic care, only 2, or 3.44 per cent, died. One of these the infant before mentioned as having a strongly positive Wassermann reaction after treatment, died at the age of sixteen months from arsenic poisoning following an injection of sulpharsphenamine in the third series of treatment. The twin sister of this child died a short time afterward at home from what was probably bronchopneumonia.

TABLE IV
INFLUENCE OF TREATMENT ON WEIGHT

	NUMBER OF INFANTS	AVERAGE WEIGHT AT SIX MONTHS	AVERAGE WEIGHT AT TWELVE MONTHS
Normal	200	4025	6100
Sulpharsphenamine	43	3760	6035
Stovarsol	8	3780	6645

Improvement in general body tone and weight is always noted in syphilitic infants while under treatment. In Table IV the average gains made during six months and one year are noted. The average listed under the heading "normal" was obtained from all of the non-syphilitic infants brought to the clinic during the past two years. Gains during the first six months are very much alike in each group, while the average gain for the whole year made by the infants who received stovarsol is over 500 grams greater than the gain for the nonsyphilitic group for the same length of time. It must be remembered that this group treated with stovarsol is much smaller in number than either of the other groups. Improvement was often noted as soon as stovarsol was started, while these same infants did not do particularly well during the six-week rest periods. Increase in appetite and activity was frequently reported by the mothers.

Tezner,⁵⁰ noting the marked improvement in treated syphilitic infants, advocated the use of stovarsol in dystrophic and poorly thriving nurslings. Lesser and Soldin⁴⁰ especially emphasized the gain in weight of syphilitic infants treated with stovarsol and traced this to the favorable effect of the arsenic. Von Mettenheim²¹ states that besides the specific effect of stovarsol on syphilitic lesions, the drug has a tonic effect. He found in the 18 infants which he treated, that the weight and general health improved, and the hemoglobin rose rapidly. Niederwieser⁴⁰ used stovarsol in nonsyphilitic infants suffering from anorexia and loss of weight and reported good results. Bratusch-Marrain⁴⁸ emphasized the good effects of spirocid treatment upon the physical development of those infants so treated. Juarros and Galarreta,⁴¹ in treating 40 older children with spirocid, reported that the most constant effect of the drug was an increase, sometimes very accentuated, in weight and height. Tuseherer⁴¹ observed that children with congenital syphilis, except those with severe visceral lesions, improve physically during the course of treatment with stovarsol, which he attributes to the arsenic. He found that the weight curves resembled those of healthy infants.

TOXIC SYMPTOMS RESULTING FROM STOVARSOL

All observers note that toxic effects from arsenic are less marked in infants than in older children. Soldin and Lesser⁴⁰ reported mild

Hierxheimer reactions in infants as did Krombach⁵¹ After the drug was discontinued for some time, it was well tolerated again

Toxic symptoms resulting from stovarsol or spirocid occur frequently, but they are usually mild In infants the most frequent toxic manifestations are diarrhea, vomiting, cutaneous symptoms, and fever Diarrhea has been noted by many observers Krombach⁵² reported occasional attacks in infants that she treated Guillemot⁵³ noted that slight digestive disturbances occurred frequently Huber⁵⁴ reported that 3 infants out of 16 treated developed diarrhea Bratusch Marain stated that some infants receiving his customary dosage showed frequent and thin stools, but these never took on an alarming character, and always disappeared rapidly after the drug was discontinued Abt and Traisman,⁵⁵ and Maxwell and Glaser⁵⁶ have noted mild diarrheas in some of the infants they treated

Exanthems of a morbilliform and scarletiform type have been frequently noted as have urticarial and bullous lesions

Transient albuminuria has been found by Abt and Traisman,⁵⁵ and Maxwell and Glaser⁵⁶ The latter authors treated 2 infants who developed a generalized flaccidity, one of whom died

In the 32 premature infants that I have treated with stovarsol there have been three who developed a mild diarrhea In each case this has occurred during the fifth or sixth week of therapy after a total dosage of from 2.5 to 3 grams of the drug The looseness of the stools ceased shortly after the withdrawal of the medication, and treatment was started again after a lapse of one week, with no further upset

Two infants developed an urticarial rash on the extremities which disappeared within one week after temporarily discontinuing the drug

One infant twenty four days old, developed a diffuse redness of the skin over the face, trunk, and extremities, which was followed by a generalized desquamation No constitutional symptoms accompanied this and the infant gained four hundred grams in the two weeks that the desquamation continued

In most cases it has been difficult for the mothers to obtain regular specimens of urine from the infants treated A trace of albumin was noted transiently in 11 of 20 infants and children whose urine was examined No abnormal microscopic findings have accompanied this albumin, and it has not been considered a contraindication to the continued use of the drug

COMMENT

The earlier antisyphilitic treatment is started in congenital syphilis, the better the chances for a normal infant and a serologic cure Many infants who have congenital syphilis do not show signs early, and often the early signs are so mild that it is difficult to interpret them An extensive review of the literature reveals that it is considered

wise, particularly abroad, to subject all offspring of syphilitic parents to prophylactic therapy, especially where there has been a recent infection, and where mothers did not have sufficient antenatal treatment. It is difficult and probably wrong to label a child from such a parent as syphilitic without clinical or laboratory evidence of the disease, but if one is to wait for this evidence, much valuable time may be lost, resulting in the failure to secure as good results as might have been obtained through early treatment. Where treatment involves the use of intramuscular injections, it is impossible not to brand the child as syphilitic, while if a peroral form of treatment can be used, it is simple to advise and employ this form of therapy without stigmatizing the child. It is extremely difficult to have patients return regularly for injection therapy, while no lack of cooperation has been evidenced with the simple dispensing of the stovarsol tablets. When the parents can actually see an improvement in the infant as far as gains in weight and body turgor are concerned, occurring during such periods of therapy, they are usually anxious to come to clinic regularly for the medication.

While in all probability many of this group of infants did not have syphilis, the mortality of only 3.44 per cent is evidence that the prophylactic treatment has been of great value. The Wassermann reaction in all infants and children so treated has been negative, and no later signs of syphilis have as yet occurred.

SUMMARY

1. At least two years of treatment, either prophylactic or curative, is advised for all premature offspring of syphilitic parents.

2. Fifty-eight infants have been treated prophylactically or curatively for congenital syphilis. Of these 8 have received stovarsol alone, 7 have had mercuric and chalk in conjunction with stovarsol, and 43 have had mercuric and sulpharsphenamine. Of the latter group, 17 have had stovarsol in their second year of treatment.

3. While no attempt is made to compare the results obtained by either form of therapy, stovarsol by mouth is advised because of its ease of administration, and the resulting cooperation of the parents.

4. No serious toxic symptoms have resulted from the use of stovarsol.

5. Early treatment has resulted in a known mortality of only 3.44 per cent of the infants discharged from the premature station to their homes, 27.9 per cent of the total 118 having died during their original admission to the hospital.

The stovarsol used in this study was furnished through the courtesy of Merck & Co.

REFERENCES

1. Lyon, Edward C., Jr., and Bemis, George Gordon. *Am. J. Obst. & Gynec.* 21: 373, 1931.
2. Kehler, E. *Zentralbl. f. Gynäk.* 47: 226, 1923.

- 3 Crawford W H Arch. Pediat. 48 293 1931
- 4 McCord J R J A M A 88 616 1921
- 5 McCord, J R. Am. J Obst. & Gynec 13 100, 1927
- 6 McCord, J R. Tr Am. Gynec Soc. 54 50 1929
- 7 Pye-Smith E J J Obst & Gynec. Brit. Emp 38 578 1931
- 8 Cruikshank, J N Medical Research Council Report No 82 1924
- 9 Funkhouser W L, and Dickson, R W Am J Syph. 12 542, 1928
- 10 Belding David L. Am. J Syph. 11 73 1927
- 11 Jeans, I C J Pennsylvania Med. Soc 33 47 1929
- 12 Bartholomew R A J A M A 83 172 1924
- 13 Wile, U J and Shaw J W J A M A 95 1501, 1930
- 14 Baumm H Zentralbl f Gynäk. 47 164 1923
- 15 Coler Eugene S Ven. Dis. Inform. 11 293 1930
- 16 Hess Julius H Premature and Congenitally Diseased Infants, Philadelphia, 1922 Lea and Febiger
- 17 Williams, J Whitridge Obstetrics ed. 6 New York, 1930 D Appleton & Co
- 18 Lawrence, Joseph J J A M. A. 82 125, 1924
- 19 Bratsch Marrain A München med Wehnschr 72 1109 1925
- 20 Adair, Fred L. Am J Obst & Gynec. 23 111 1932.
- 21 von Mettenhelm H. Med. Klin 27 422 1931
- 22 Atlee Edward A. and Tyson, Ralph M: Am. J Dis. Child, 44 718 1932.
- 23 McCord J R. Am. J Syph. 12 181 1928
- 24 Dunham Ethel C Am J Dis Child. 43 311, 1932.
- 25 Kolmer John A Arch Pediat 37 129 1929
- 26 Taylor Charles B J Oklahoma M A 23 301 1930
- 27 Klaffen E. Zentralbl f Gynäk 51 400 1921
- 28 Klaffen E. Klin Wehnschr 7 458 1923
- 29 Hoffman, Erich Monatschr f Geburtsh. u. Gynäk. 84 122, 1930
- 30 Nabarro David Brit J Ven Dis. 7 1 1931
- 31 Marfan A. B Presse méd. 31 373 1923
- 32 Pillsbury, Donald M Internat. Clin. 2 236 1931
- 33 Scherber G Wien. klin. Wehnschr 40 909 1921
- 34 von den Steinen, R München. med. Wehnschr 74 1006 1927
- 35 Lereboullet, P Progrès méd. 40 118, 1925
- 36 Bona, H Handb d Haut u. Geschlechtskr 19 327 1927
- 37 Buschke A. and Gumpert Martin Klin Wehnschr 6 103 1927
- 38 Hahn, R. Prakt. Arzt 16 249 and 277, 1931.
- 39 Maxwell C A., Jr., and Glaser Jerome Am J Dis. Child. 43 1461 1932.
- 40 Soldin Max and Lesser, Fritz Deutsche med Wehnschr 54 958, 1928
- 41 Tascherer J Monatschr f Kinderh 45 62 1929
- 42 Oppenheim M., and Fessler A Arch. f Dermat u. Syph 156 549 1928
- 43 Courtin W Arch. f Kinderh. 91 250 1930
- 44 Krosi, H. Wien. klin. Wehnschr 37 1200 1924
- 45 Müller Erich Arch. f. Kinderh 91 108 1930
- 46 Wegner E. Dermat. Ztschr 57 178 1929
- 47 Bieschmann G: Hospital 20 3 1930
- 48 Bratsch Marrain, A Arch f Kinderh 92 26 1930
- 49 Abt Arthur F., and Traisman, Alfred S. Paper delivered before the Chicago Pediatric Society October 1932 (Unpublished.)
- 50 Rosenbaum Harold Am J Dis Child. 44 25 1930
- 51 Nodelmann E Jahrb f Kinderh 134 80 1931
- 52 Krombach K. Klin Wehnschr 7 1512 1928
- 53 Lewin, G Med. Klin. 87 470 1931
- 54 Fürst, Kurt Jahrb f Kinderh. 69 335 1928
- 55 Husten C: Arch f Kinderh. 69 319 1931
- 56 Antoniewicz V R. Vrach. gaz. 12 933 1930
- 57 Lange R Jahrb f Kinderh 90 83 1930
- 58 White P J., and Veeder B Am. J Syph. 6 353, 1929
- 59 Texner O Monatschr f. Kinderh. 34 6, 19 G.
- 60 Niederwieser V Wien klin. Wehnschr 42 741 1929
- 61 Juarros, C. and Galarreta P Siglo med. 80 653 1927
- 62 Guillemot L. Bull Soc. de pédiat de Paris 22 211 1924
- 63 Huber H G Med. Welt 4 1331 1930
- 64 Abt, Arthur F and Traisman, Alfred S J PEDIAT 1 172 1932.

GROWTH PROBLEMS

II BASAL METABOLIC RATE VARIATIONS IN RELATION TO BODY BUILD ADOLESCENCE AND ALLERGY IN CHILDREN

WILLIAM PALMER LUCAS, M D, HELEN BRENTON PRIOR, M D, CRAWFORD
BOST, M D, AND SANTON T POPE, JR, M D
SAN FRANCISCO, CALIF

A STUDY of 1,334 basal rate determinations on 680 normal children shows every gradation from high to low rate. The rates plotted follow a typical normal distribution curve similar to the distribution curves of any other biologic data in a large series.

Symmetrical variation above and below the average is seen in the normal distribution curve of any trait, the majority of cases being classified *normal*, whether the data are height or oxygen consumption or introversion. It is necessary to plot the entire curve of distribution in order to recognize degrees of deviation, and the total curve should be kept in mind in diagnosing *normal* functions for any individual.

BODY BUILD FACTOR IN BASAL METABOLISM

Parallel studies of basal metabolic rate and body build in 415 children¹ showed a definite relationship between thyroid activity and type of body build. High basal rates were the rule for the slender-built and low basal rates for the broad-built. Oxygen consumption was compared with body build by means of the Pearson correlation coefficients. The relationship between percentage deviations from average calories per kilogram body weight per hour, and from average width-length index of build for age and sex were as follows:

177 boys	Ages 3-17 years	$r^* = -0.196$	± 0.049
238 girls	Ages 3-17 years	$r = -0.262$	± 0.041

These negative correlations showed that degrees of slenderness below average of body build were related to degrees of increase above average in oxygen absorption in this group of 415 children. In other words the difference in relative width of the body (measured by the width-length index) seemed to be a determining factor in oxygen absorption when both were on a unit basis.

Our approach in the present study, being medical and not surgical, has employed the basal metabolic rate as its method for recognizing levels of glandular function. Consequently, the classification of the children has been in terms of basal metabolic rate variations. Recognizable pathologic thyroid abnormalities have been excluded from this study.

* r equals the Pearson coefficient of correlation

If biopsy were feasible we wonder if even these remaining thyroids might not show histologic staining differences consistent with varying degrees of secretory activity. We have considered this series to represent hypo- and hyperfunction without hypo and hyperplasia. We have not seen any progressive tendency toward the pathologic entities.

What determines the levels of glandular activity is debatable, although suspicion falls strongly on inheritance. Physical type, however, seems to be almost invariably a consequence of glandular state.

The groups called linear and lateral undoubtedly are to be associated with thyroid hyper and hypofunctions respectively and the body changes induced by extreme gross pathologic thyroid states are unquestioned and diagnostic.

Our basal rates were referred to the Benedict Talbot standard. They were done after one half hour rest in the postabsorptive state, and represent at least two consecutive determinations that check.

HIGH BASAL METABOLIC RATES IN SLENDER CHILDREN

One hundred and ten of our 680 children had basal metabolic rates of 20 per cent plus and over but exhibited none of the cardinal toxic

TABLE I

HIGH BASAL METABOLIC RATES IN SLENDER BUILT CHILDREN

CASE NO	AGE	SEX	W L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIES PER HOUR
81	4	F		-30.0	+54.0	39.0
5a	4	F		-7.4	+42.0	
504	5	F	-7	-21.0	+28.8	39.7
141	6	M	-1	-8.9	+29.0	49.0
558	6	M	-6	-15.3	+29.0	46.3
	6			-11.7	+25.1	46.7
491	6	M		-18.0	+31.0	50.7
443	6	M		-3.0	+38.4	51.5
155	8	M	-5	-12.6	+33.0	47.5
406	8	F		-21.0	+36.8	50.1
	8			-13.5	+25.7	51.7
72	8	F	+3	-8.7	+15.1	49.2
160a	8	M		-9.5	+37.3	
340a	9	F	-6	-1.8	+44.0	52.4
49	9	F	-1	-15.0	+64.8	5.5
87a	10	F	-3	-5.9	+23.0	52.3
322	12	F		-16.4	+20.0	63.8
412	16	F	-1	-18.3	+24.0	68.5

The Width-Length Index variation shows relative breadth, or percentage broader or narrower than average, for the age, sex, group.

Variation from average weight shows the percentage underweight referred to the Baldwin-Wood standard.

B.M.R. is the Basal Metabolic Rate referred to the Benedict Talbot scale.

signs of hyperthyroidism, such as tremor, exophthalmus and other eye signs hyperhidrosis, and polyphagia. They were however high strung easily fatigued children and often had rapid pulses. The

GROWTH PROBLEMS

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These negative correlations showed that degrees of slenderness below average of body build were related to degrees of increase above average in oxygen absorption in this group of 415 children. In other words, the difference in relative width of the body (measured by the width-length index) seemed to be a determining factor in oxygen absorption when both were on a unit basis.

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* r equals the Pearson coefficient of correlation

"Statistics also show that there is a relation between the height and weight and the heart rate in children of the same age, in the sense that the heart rate tends to be slower in children of larger stature." This is shown in the accompanying table by Volkmann

RELATION OF HEART RATE TO BODY LENGTH AT DIFFERENT AGES (VOLKMANN)

AGE	SMALL CHILDREN	LARGE CHILDREN
1	146.5	123.1
2	124.0	111.0
3	113.2	104.3
4	111.7	110.2
5	106.0	102.3
6	102.5	99.9
7	101.0	93.8
8	97.0	98.0
9	90.0	89.0
10	93.0	88.0
11	88.5	8.0
12	91.3	81.0
13	87.6	81.0
14	89.1	80.3
15	81.0	81.0

Recent work³ indicates that the normal body temperature is higher for young children than for adults. Dr. Stolz and Miss Ludwig at the Institute of Child Welfare, University of California, have studied variations in body temperature in healthy pre-school children. Rectal temperatures were taken at nine and eleven o'clock in the morning and at one and three o'clock in the afternoon each day on 18 children. They reported that each child had his own range of temperature. In one child the average of all temperature readings was as high as 100° F. and another as low as 99.2° F. The average for the total series of records was 99.5° F. which is distinctly higher than the rectal temperature of 98.96° F. which Howell reports as normal for healthy adults.

Jenkins⁴ reported mean body temperatures taken at the time of basal metabolic rate determinations for 846 men to be 97.7° F., and for 2,408 women to be 98.1° F. These were mouth temperatures, and are a little lower than Howell's figures.

Jenkins' material indicates that a 'rise of one degree Fahrenheit is equal to a rise in the basal rate of seven per cent in the case of men, or five per cent in the case of women. One degree Centigrade is the equivalent of twelve per cent for the men and nine per cent for the women.' Dubois reports 7.2 per cent for each degree Fahrenheit or 13 per cent for each degree Centigrade.

Because the pulse rate is normally higher, and the body temperature is normally higher, at the younger age levels, both of these facts seem logically in keeping with higher basal metabolic rates in young children, since rapid pulse and wasteful rate of oxidation are associated with an overactive thyroid gland.

Our findings would tend to agree in theory with Jenkins' basal pulse complex and with the prediction formula of Read,⁶ although to date we have not made use of these methods

The clinical application of these facts may be helpful in understanding a certain type of persistent low-grade febrile state which often reaches the pediatrician. After negative physical examinations, negative intradermal tuberculin tests, and negative roentgen studies, children with this complaint frequently remain under suspicion of obscure infection, usually pulmonary or lular.

Several observers⁷ have reported a prepuberal rise in the basal metabolic rate. Inasmuch as our figures show basal rates much higher for preadolescent than for adolescent children, we wonder if the apparent prepuberal rise is not because the first observations were made at ages nine to ten instead of at ages five to six years. The averages of 1,334 first satisfactory basal rate determinations by age and sex for our 680 children are as follows:

AGES	BOYS		GIRLS	
	NUMBER CASES	AVERAGE BASAL METABOLIC RATE	NUMBER CASES	AVERAGE BASAL METABOLIC RATE
3-5	31	plus 16.91%	35	plus 11.42%
6-9	137	plus 10.71%	162	plus 8.53%
10-17	141	plus 0.25%	176	plus 2.58%

It will be seen that there is not only a prepuberal rise, but that there is a consistent and continual rise as the age level recedes to early childhood.

Consequently, it may be stated more accurately that the basal metabolic rate decreases regularly from early childhood to adolescence.

BASAL METABOLIC RATE VARIATIONS DURING ADOLESCENCE

The so-called distorted energy requirement of adolescent children is illustrated in the widely variant basal metabolic rates obtained during this period. The unusual activity and demands made by rapid growth is offered as explanation. Table V shows a serial study of basal metabolic rates on 26 of our adolescent children. Wide fluctuations in rate and rapid swinging from plus to minus or minus to plus were characteristic of this group.

Blunt, Tilt, McLaughlin and Gunn⁸ studied 46 girls aged nine to eighteen years at yearly intervals. They state that neither the average figures for the different ages, nor the variation in their few individual girls showed any effect of puberty.

Gardner and Brett⁹ in a study of adolescent goiter compared physical measurements of one hundred cases of colloid goiter with average standards for height and weight. They reported that a large majority

TABLE II

WIDE FLUCTUATIONS IN BASAL RATES DURING ADOLESCENCE ILLUSTRATE THE
"DISTORTED ENERGY" REQUIREMENT

CASE NO	AGE	SEX	W L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIES PER HOUR
290a	10-0	M	-6	-11.0	+18.0	53.0
	11-0			-10.0	+25.9	59.4
	11-3			-11.3	+4.5	48.6
	11-6			-10.8	+11.6	53.7
108	11-5	M	+1	-0.3	+2.7	56.0
	11-8			-12.0	-21.0	45.7
	11-9			-12.0	+13.1	41.0
	11-11			-15.6	0.0	44.7
	12-6			-16.3	+21.9	63.4
	12-8			-15.7	+15.7	64.1
	13-0			-17.0	+2.0	59.0
	13-5			11.4	+11.0	
503	11-9	M	+2	+13.7	+23.8	60.0
	12-4			+10.4	-9.0	51.3
	12-7			+1.3	-10	50.6
392	10-4	M	+0	+31.0	-16.4	46.0
	10-7			+10.4	0.0	51.4
	12-8			+22.7	-2.0	66.0
	12-10			+23.6	+15.5	57.8
437	12-0	M	+6	+11.1	-14.2	40.5
	12-6			0.0	-7.2	51.5
	13-0			0.0	-21.0	45.4
	13-0			+4.5	-0.4	57.8
403	11-0	M	-1	+14.8	-10.2	48.0
	11-4			+21.5	-12.0	48.1
	11-0			+21.2	+2.7	50.6
	11-4			+30.0	-10.7	53.9
540	9-5	M	-1	-12.6	-10.0	30.8
	9-8			-11.1	+5.5	45.9
	9-11			-9.9	-5.7	42.9
	10-8			-4.0	+23.8	60.7
	11-1			-3.2	+7.2	53.2
84	9-0	F	-7	-25.0	+21.7	1.6
	10-0			-7.2	+4.0	50.6
	10-1			-7.7	-4.7	46.0
	10-4			-5.1	-12.8	43.9
	11-4			-16.0	+9.0	66.4
	11-7			-11.0	+5.5	64.3
	11-10			-14.0	+18.3	54.6
410	9-8	F	+2	+12.1	0.0	51.0
	10-2			+10.9	-8.5	49.0
	10-6			+7.0	-18.0	41.8
	11-0			+5.0	0.0	50.8
	11-7			+9.6	+16.9	60.7
	12-0			+15.6	+11.8	58.4
410	11-1	F	+3	+40.0	-8.2	48.4
	11-7			+13.6	+1.0	52.3
	12-7			+24.5	+7.1	56.9

The Width Length Index variation shows relative body width, or percentage broader or narrower than average, for the age, sex, group.

Variation from average weight shows the percentage overweight or underweight referred to the Baldwin Wood height-weight table.

B.M.R. is the Basal Metabolic Rate referred to the Benedict Talbot scale.

Benedict Hendry Baker and Aub Dubois standards were used for a few cases.

TABLE II—CONT'D

CASE NO	AGE	SEX	W L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIFS PER HOUR
547	11-	F	-6	- 5 4	-20 8	34 4
	12-			+ 9 1	+ 9 1	55 8
	13-			0 0	+10 2	56 2
151	13-5	M	+5	+14 1	+ 5 3	72 2
	13-7			+10 4	+ 9 5	75 8
	13-9			+12 4	- 7 8	63 7
	14-3			+10 0	- 7 2	65 3
337	12-10	M	-8	-14 1	-26 7	40 0
	13-2			0 0	-29 0	43 0
	13-8			- 9 0	-15 8	50 4
	14-2			-13 7	-10 8	54 5
202	12-2	M	-2	- 4 7	-11 8	47 6
	12-8			- 3 0	-13 1	48 1
	13-0			- 7 6	+13 9	64 6
	13-6			- 5 0	-13 0	52 6
	14-0			- 2 3	0 0	63 7
389	11-10	M	+1	-10 0	+11 8	60 3
	12-1			- 3 6	+ 9 9	60 2
	12-3			- 3 0	+ 5 9	60 2
218	12-6	M	+3	+13 8	+ 1 3	52 2
	13-0			+ 8 0	-12 8	47 4
	13-2			+ 8 0	-18 0	57 3
	14-5			+12 7	+ 2 6	61 6
246	10-2	F	-2	+ 9 0	- 5 0	64 4
	10-8			+ 2 0	+23 0	48 4
	11-0			- 6 6	+ 2 3	53 2
	11-11			- 8 6	- 5 8	
188	11-3	F	+2	- 8 6	+10 1	45 2
	11-7			- 7 6	+11 3	47 1
	12-9			- 3 6	-10 5	38 1
56	10-3	F		+34 0	-22 0	
	11-4			+ 9 0	-23 0	
	12-0			+ 6 0	+ 2 0	54 4
	12-1			+10 8	+ 3 2	55 5
253	10	F	+5	+21 8	+27 7	67 2
	11			+30 0	+18 3	63 3
	12			+31 5	- 9 2	79 7
	13			+22 8	-19 0	79 3
326	10-8	F	+5	+18 0	+18 0	53 6
	11-7			0 0	- 9 5	43 7
	13-1			- 5 8	+15 1	57 7
332	10-8	F	+16	+23 0	-27 0	
	11-0			+23 0	-19 0	
	11-6			+27 1	+34 6	71 9
	11-9			+24 5	+ 9 6	58 8
	12-6			+23 8	-18 4	51 0
	13-0			+ 8 0	+16 0	61 8
	13-5			+ 4 4	- 2 8	51 6
364	11-5	F	+5	+ 5 2	+ 5 2	54 4
	12-0			+ 3 7	+ 8 8	46 8
	14-1			- 5 0	+26 9	66 7
	14-3			- 5 9	+11 0	57 8

TABLE II—CONT'D

CASE NO.	AGE	SEX	W L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIES PER HOUR
372	10-2	F	-1	-11.1	-14.8	30.2
	10-0			-3.8	+9.6	51.8
	11-0			-2.1	-10.3	43.3
	11-3			-0.3	-12.9	43.7
	11-6				-4.5	
181	10-2	F	-6	-8.0	-3.3	43.9
	10-9			-9.0	+25.4	59.3
	11-4			-5.7	+30.2	66.7
445	12-	F	-12	-17.2	+9.8	51.5
	13-			-12.5	+33.5	68.4
	13-			-9.0	+7.1	55.1
	14-			-11.5	+28.1	65.9

of children with goiter were above average height for their age. Their hyperthyroid patients were below average weight for age and height. Their hypothyroid patients were above average weight for age and height.

Stocks, Stocks, and Karn¹⁰ reported a similar finding with a possible explanation as follows: "Goiter tends to appear more readily or to become more pronounced in relation to the child's size (in girls whose heights are above average for their ages) or girls whose thyroids enlarge about puberty tend in consequence to grow more rapidly in height." The authors incline toward the first explanation.

Holmgren¹¹ in 1910 studied the growth spurt at puberty. He thought that rapid growth in height at the time of puberty was likely to produce a hyperthyroid reaction. In 1929 Thomas¹² stated that this conjunction of high metabolism with hyperthyroidism and rapid growth indicated that the thyroid hormone which stimulates metabolism was identical with the growth-accelerating hormone of the thyroid.

FACTORS IN LOW BASAL METABOLISM

Fasting has been shown to lower the basal metabolic rate. Talbot's¹³ study of fasting in cases of idiopathic convulsions in children in 1925, demonstrated definite reduction in metabolism. Schick and Cohen¹⁴ the same year studied convalescent children and reported that a low basal metabolic rate followed the exhaustion of fevers and infections and might last from one to several weeks. They believed that the low pulse characteristic of early convalescence was caused by the low metabolism.

Since higher basal metabolic rates are characteristic and normal for young children, all minus rates should receive careful attention as indicating a deviation toward an abnormal glandular condition. Inspection of the mean basal metabolic rates for this series indicates that any minus rate in a preadolescent child is below the accepted limits of normal, when the correction factor of minus 11.5 per cent is applied.

Examples are given in Table III where the basal rates when corrected with minus 115 per cent are all distinctly low

TABLE III
PREADOLESCENT CHILDREN WITH SLIGHTLY MINUS BASAL RATES

CASE NO	AGE	SEX	W L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIES PER HOUR
279	6	F	+3	+ 4 2	-3 6	34 5
258	7	M	-3	+ 4 4	-1 3	42 7
128	9	M	-3	+ 6 0	-2 8	44 3
115	8	F	+4	+ 4 3	-2 0	39 6
100	9	F	-5	+18 1	-4 1	41 2
101	4	M		+11 6	-1 5	36 1
102	8½	F	-4	+ 5 0	-1 5	39 2
153	7	F	+1	+ 4 2	-3 9	45 2
264	9	F	+1	+31 0	-4 0	49 5
295d	9	F		+17 0	-4 6	43 2
125a	8	F	+4	+17 7	-2 4	45 4
498	7	F	+7	+10 9	-1 2	43 0
427	5	F	+2	+ 1 0	-3 6	31 9

The Width-Length Index variation shows relative breadth, or percentage broader or narrower than average for the age, sex, group
Variation from average weight shows the percentage overweight referred to the Baldwin-Wood standard

B.M.R. is the Basal Metabolic Rate referred to the Benedict-Talbot standard

Children below ten years of age with basal metabolic rates no lower than minus three or minus four (Benedict-Talbot standard) tend to put on weight readily and to be sluggish. These show marked improvement with a little thyroid therapy.

TABLE IV
LOW BASAL METABOLIC RATES IN BROAD-BUILT CHILDREN

CASE NO	AGE	SEX	W L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIES PER HOUR
409	3	F	+10	+13 8	- 9 4	27 6
	4			+54 0	-23 3	30 9
	4			+27 0	-11 0	33 3
	5			+32 7	-21 8	30 6
349	6	M	+1	+12 6	-23 7	32 5
331	6	F	+1	+25 0	- 9 8	45 0
454a	6	F	+2	+24 5	- 6 5	40 2
318	7	M	+4	+18 6	-19 4	40 7
45	8	F	+4	+20 0	- 4 8	43 0
	8			+11 0	0 0	40 6
543	8	F		+28 0	- 7 1	46 6
154	9	M	-3	+28 7	-25 4	38 3
295b	10	M	+2	+28 8	-19 4	46 1
9	10	F	+5	+18 8	-18 5	42 2
450	12	F	+12	+25 2	-26 0	56 5
506	13	F		+48 1	-27 7	62 4
190	14	F	+13	+21 3	-19 6	56 5

The Width-Length Index variation shows relative breadth or percentage broader or narrower than average for the age, sex, group
Variation from average weight shows the percentage overweight referred to the Baldwin-Wood standard

B.M.R. is the Basal Metabolic Rate referred to the Benedict-Talbot standard

Twenty eight of our cases in which the basal metabolic rate was very low were more overweight than the above group, and these children appeared with an entering complaint of obesity. Several of this group shown in Table IV were very broad built with large width length indices and all appeared to be markedly overweight. Their basal metabolic rates were low and became very low when corrected with minus 11.5 per cent. These children require thyroid treatment for a much longer period of time than the group in Table III, and need to stay on a restricted diet. They lose weight quite readily while taking thyroid and most of them feel much better on thyroid than when not taking it. This group shows the extreme of the low variations and is close to the borderline of pathologic hypothyroid cases.

Very broad built children often have low basal metabolic rates and come in complaining of being overweight when they are not very much overweight for their build.

ANOMALOUS LOW BASAL RATES IN SLENDER UNDERWEIGHT CHILDREN

Dr Hoskins¹³ of the neuro endocrine research department at Harvard reported "In addition to the sluggish, myxedematous type of deficiency as just described, there has come to be recognized in recent years

TABLE V
LOW BASAL METABOLIC RATES IN CERTAIN SLENDER BUILT CHILDREN
WHO ARE OFTEN ALLERGIC

CASE NO.	AGE	SEX	W L INDEX VARIATION IN PER CENT	VARIATION FROM AVERAGE WEIGHT IN PER CENT	B M R. PER CENT	CALORIES PER HOUR
244	6	F	-7	-11.5	-9.7	80.7
41	7	F	+1	-6.0	-7.6	38.9
558b	-	M	-1	-11.2	-11.3	36.6
107	8	F	-2	-8.8	-19.3	29.8
374	8	M	+3	-11.8	-13.8	38.5
215	8	M		-7.8	-12.0	35.7
	9			-2.1	-8.5	43.6
562	9	M		-17.8	-11.3	38.8
394	10	M		-6.3	-20.7	39.5
20	11	F		-12.8	-17.0	35.5
96	11	M		-14.0	-12.7	42.1
88	12	F	+5	-3.5	-19.9	42.5
416	13	M	-7	-7.8	-12.5	53.5
8c	16	M	-2	-17.8	-17.0	43.7
532	18	F	+2	-10.0	-18.7	45.2
	18			-10.1	-3.4	50.6

The Width-Length Index variation shows relative breadth of body or percentage broader or narrower than average for the age sex group.

Variation from average weight shows the percentage overweight referred to the Baldwin Wood standard.

B.M.R. is the Basal Metabolic Rate referred to the Benedict Talbot standard.

a thin, irritable nonmyxedematous type. The subjects, far from being phlegmatic, are overresponsive to environmental annoyances. The causal relationship of thyroid deficiency to the condition is indicated

by the marked diminution of the basal metabolic rate and is proved by increase of weight and restored placidity of disposition under thyroid medication "

Topper and Mulier¹⁶ reported a group corresponding to one of ours that was underweight with low basal metabolic rates

We have 67 cases showing moderately low basal metabolic rates in children, the majority of whom are slender-built and all of whom are under average weight referred to the Baldwin-Wood standards. These children might be expected to have high basal metabolic rates, both because of age and body build. Table V illustrates this group which deviates in the unexpected direction in basal metabolic rate. We have tried to find out what other things they share in common.

As a group they are fairly quiet youngsters with a heightened upper respiratory susceptibility. A large proportion of them (46 out of 67) are also allergic. (Their upper respiratory susceptibility may be on an allergic basis.) Upon examination, allergy was the most suggestive common denominator. Consequently, a direct analysis of our allergic children for whom basal rates were available, was undertaken to demonstrate, if possible, any existent metabolic trend.

BASAL RATES IN ALLERGIC CHILDREN

Out of a group of 72 allergic children, 58 had minus basal metabolic rates when corrected for age. The other 14 ranged from plus 12.1 per cent to plus 1.8 per cent. The average basal metabolic rate for the 72 was minus 5.8 per cent. The tendency of the group therefore was toward low basal metabolic rates.

Table VI shows the relationship between allergy and basal metabolic rate by age.

TABLE VI

THE BASAL METABOLIC RATE IN 72 ALLERGIC CHILDREN, 26 OF WHOM HAD MULTIPLE MANIFESTATIONS

AGES	ASTHMA			ECZEMA			HAY FEVER			URTICARIA			GASTROINTESTINAL ALLERGY		
	NO CASES	NO B.M.R.	AVERAGE B.M.R.	NO CASES	NO B.M.R.	AVERAGE B.M.R.	NO CASES	NO B.M.R.	AVERAGE B.M.R.	NO CASES	NO B.M.R.	AVERAGE B.M.R.	NO CASES	NO B.M.R.	AVERAGE B.M.R.
0-3	2	2	minus 17.2%	1	1	minus 19.9%									
4-6	16	25	minus 4.9%	6	9	plus 5.3%	6	11	minus 8.1%	1		plus 27.2%			
7-9	12	18	minus 9.8%	4	5	minus 1.6%	11	20	minus 5.7%	6	9	plus 4.0%	3	9	plus 11.1%
10-15	12	33	minus 4.8%	4	9	plus 1.3%	14	39	plus 0.6%	2	5	plus 1.0%	2	3	plus 3.6%
Total	42		minus 6.43%	15		minus 4.22%	31		minus 3.32%	9		plus 5.91%	5		plus 8.1%

Presented by age groups and showing averages compiled from 198 B.M.R. determinations on allergic cases.

Not all of our allergic children were slender built with low basal metabolic rates. The babies with eczema were broader than average and for them metabolic studies are lacking.

Measurements to classify body build were done on 97 allergic children. The younger children had more eczema and the older ones more asthma and hay fever. See Table VII for the classification by age, sex and build.

TABLE VII

BODY BUILD IN 97 ALLERGIC CHILDREN 23 OF WHOM HAD MULTIPLE MANIFESTATIONS

AGES	ASTHMA		ECZEMA		HAY FEVER		URTICARIA		GASTROINTESTINAL ALLERGY	
	NO CASES	AVERAGE BUILD	NO CASES	AVERAGE BUILD	NO CASES	AVERAGE BUILD	NO CASES	AVERAGE BUILD	NO CASES	AVERAGE BUILD
0-3	4	3.0% Narrow	9	0.6% Broad	2	1.0% Narrow	5	0.2% Broad	3	1.6% Broad
4-10	18	3.5% Narrow	7	1.3% Broad	7	Exactly Average	1	2.0% Broad	1	2.0% Broad
7-9	11	2.0% Narrow	2	0.5% Broad	8	3.1% Narrow	4	3.7% Broad	5	5.0% Broad
10-15	16	4.4% Narrow	3	0.7% Broad	14	8.6% Narrow	1	11.0% Broad	3	0.7% Broad
Total	49	8.4% Narrow	21	0.6% Broad	31	2.4% Narrow	11	2.1% Broad	10	1.3% Broad

Presented by age groups and showing average body build in terms of percentage broader or narrower than the mean for age and sex.

The total allergic group averages .16 per cent narrow.

Body measurements to distinguish build were recorded in terms of percentage broader or narrower than average for age and sex. The children with asthma and hay fever were consistently slender built with minus basal metabolic rates. Those with eczema were slightly broader than average and had variable basal rates. The children with urticaria and gastrointestinal allergy showed no consistent type of body build and their basal rates as a group ranged above average.

Whether there is a causal relationship between low basal metabolic rates and certain allergic tendencies in children is a question that merits further study. At the present time we can say only that in our group of slender built children with basal metabolic rates lower than average for their ages, and lower than average for their build 68 per cent were allergic. In addition to this 80 per cent of our allergic children, who had basal metabolic rate determinations done, had minus rates. Perhaps the constitutional factor in allergy is similar to the constitutional factor which causes the unexpected direction of variation in the basal metabolic rates.

Constitutional influences on basal metabolism are reported by the White House Conference to be

- 1 Those hereditary factors which affect body size and proportion
- 2 Those which affect nervous organization.

3 Those which produce a tendency to leanness or fatness, aside from the endocrine functions

4 The endocrine factors themselves

The report further points out that there are great varieties of body shape and size which possess normal endocrine functions and that

1 The presence of bone diminishes the metabolism per unit of mass while the presence of large amount of muscle increases it

2 A highly nervous or hysterical temperament accentuates the basal rate while a phlegmatic temperament lowers it

We have previously pointed out that broad-built children have larger bony frameworks than slender-built ones who have better muscles. Our personality and heredity studies have shown that, in general, our slender-built children are much more nervous, high-strung, and easily fatigued than our broad-built children, who are, in general, slower and more easy-going. All of these things are corroborative of the findings of the White House Conference Committee since our slender-built children consistently had higher basal rates than our broad-built ones, even though we had one group of slender children with low basal rates which were averaged with the other slender-built children.

CONCLUSIONS

1 A group study of any biologic data helps to establish trends in the general population and to diagnose normal variations for the individual.

2 The individual case cannot illustrate all the elements that make up the group classification, nor can one case meet all the requirements that result in the conclusions drawn from a group study.

3 Such a group study of 1,334 basal metabolic rates in 680 children shows every gradation from high to low rates.

4 The basal metabolic rate decreases regularly from early childhood to adolescence, where it reaches the adult level.

5 Other physiologic data, such as pulse rate and body temperature, parallel the basal metabolic rate in its age level variations, tending to emphasize the reasonableness of the finding.

6 High basal metabolic rates are characteristic of slender-built children regardless of age, and low rates are characteristic of broad-built ones.

7 Since the higher basal metabolic rates are characteristic and normal for young children, all minus rates should receive careful attention as indicating a deviation toward an abnormal glandular condition.

8 Children under ten years of age with slightly minus basal metabolic rates tend to put on weight readily and to be sluggish.

9 In our group of slender built children with basal metabolic rates lower than average for their ages, and lower than average for their build, 68 per cent were allergic. In addition to this, 80 per cent of our allergic children, for whom there were basal metabolic determinations had minus rates

REFERENCES

- 1 Lucas, W P and Pryor, Helen B. Am J Dis Child. In press
- 2 Lucas, W P Pryor, Helen B., Bost, A C, Pope S. T., and Henderson M C
J Pediatr. 1 572 1932
- 3 Stolz, H. R., and Ludwig Gladys N. Child Development 2 225, 1931
- 4 Jenkins R L. Arch. Int Med 49 181 1932
- 5 Howell, W H. Textbook of Physiology, ed 10 Philadelphia Saunders, p 980
- 6 Read, J M. Arch. Int Med 34 553 1924
- 7 Dubois, E F. Basal Metabolism in Health and Disease Philadelphia, 1927,
Lea & Febiger p 147
Topper Anne and Muller, Hannah. Am J Dis. Child 43 327 1932
- 8 Blunt K. Tilt, T., McLaughlin, L. and Gunn, K B. J Biol. Chem. 67 491 1926
- 9 Gardiner H H., and Brett P C. Quart J Med 18 133, 1925
- 10 Stocks P S., Stocks, A. V., and Karm M N. Biometrika 19 202, 1921
- 11 Holmgren J. Med. Klin 6 1047 1910
- 12 Thomas E. Handb der Inneren Sekretion 2 1291, 1920
- 13 Talbot F B and Moriarty, Margaret. Am. J Dis. Child 28 419 1924
Talbot, F B. Physiol. Rev 5 477 1925
- 14 Schick B., and Cohen P. Am. J Dis Child 30 201 1925
- 15 Hoskins R. G. The Tides of Life New York 1933 Norton, p 79
- 16 Topper Anne, and Muller Hannah. Am. J Dis. Child 43 327 1932
- 17 White House Conference on Child Health and Protection. Growth and Development Part III. Nutrition, New York, 1932, Century Co

MULTIPLE CONGENITAL RIB AND SPINAL DEFORMITIES

REPORT OF A CASE

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COMPARATIVELY little was known of rib and spinal anomalies prior to the development of roentgenology as a science and the widespread use of the x-ray in the diagnosis of bone conditions. It has become increasingly more evident that particular examples of congenital malformations of the skeleton are usually associated with other bone defects. For example, cases of absence of ribs are invariably associated with corresponding vertebral malformations.¹

Various congenital anomalies may occur in rib formation. Among these anomalies may be mentioned

Cervical ribs

Variations in size and shape

Bifurcation

Fusion

Total absence of one or more ribs

Lumbar ribs

Cervical ribs have been known for centuries. Galen (A.D. 200) mentions cervical ribs. Much has been written on this subject in recent years as many of the cases mentioned were discovered accidentally by x-ray.

White² states that of 5,728 chests examined with x-rays for various conditions other than anomalies, about 1 per cent showed congenital variations of all types. He states further that 20 cases of this series showed cervical ribs.

Henderson³ records 31 cases of cervical ribs in the routine examinations of approximately 80,000 patients. Eighteen of the 31 gave no subjective symptoms. Eleven of the 18 did not show a tumor and all had been subjected to an x-ray examination of the chest for some other reason—question of tuberculosis, for large heart, for determination of possible substernal goiter, for possible aneurysm.

Cushway and Maier⁴ found 3 men with cervical ribs of 931 applicants whose spines were filmed routinely as a check-up for any possible abnormality before they were permitted to work as switchmen.

From the Pediatric Service of the New York Nursery and Child's Hospital

Because lumbar ribs are seldom of any clinical significance, the literature makes little of this anomaly. That they occur more often than is suspected can be deduced from the fact that Cushway and Maier report, in their series, 81 patients with ribs attached to the first lumbar vertebra as compared to 3 in whom the ribs were attached to the seventh cervical vertebra.

Giles⁵ made 8,000 spine examinations and found 1,122 showing anomalies. Seventy-three of these 1,122 disclosed lumbar ribs.

Cumming⁶ reports a case of a rib arising from the transverse process of the third lumbar vertebra. The rib curved downward and fused with the transverse process of the fourth lumbar vertebra of the same side. This rib was discovered after an examination for pain in the back. The rib was fractured as the result of injury.

As to the variations in the sizes and shapes of ribs, White² found considerable variations in the size of the first rib. Sometimes the first rib was almost as thin as a cervical rib. In other cases it was broad and failed to articulate with the sternum although the corresponding cartilage was completely calcified.

Hrdlicka⁷ says that he found the third rib, particularly its sternal half, more subject to modification and the eleventh and twelfth differing much more in size than in shape.

Absent ribs have been reported by a number of observers. Steindler¹ gives a short résumé of the literature on this condition and says, "a distinction should be made between the partial defects of ribs and sternum which are comparatively common and the total defects of one or more ribs which are extremely rare."

Sever⁸ examined several thousand films which had been taken of patients in the orthopedic department of the Children's Hospital in Boston and discovered a number of cases of absent ribs.

There are not many examples of true bifurcation. Among these may be mentioned one by Bloomberg⁹ who cites a case of a boy, four years old, who had bifurcations of the third and fourth ribs on the right side.

Dennis¹⁰ cites 3 cases. 2 of the fourth right rib and 1 of the third left.

Ruppricht¹¹ discusses the case of a fetus in which he found bifurcations of the third and fourth ribs both on the right side.

Hrdlicka⁷ found 6 specimens of forking of which only one specimen was on the left side. The sternal extremity was the part affected.

Struthers¹² describes 5 specimens and Adams¹³ 3. These were all at the sternal extremity, mostly limited to the cartilage, and not very great in extent.

Fused thoracic ribs are among the uncommon anomalies Hrdlička¹³ examined 1,000 first ribs, 1,200 second ribs, and 14,000 ribs other than first and second. Of this large series, there were 4 specimens of fusion. He found 2 additional examples among ribs of American Indians. This anomaly was on the left side in 5 out of the 6. In 2 of the 6, there was a junction of a cervical with the first rib, in 3, a junction of the first and second, and in 1, a junction of the third with the fourth rib. In both cases of the union of the cervical rib with the first, and in one case of union of first with the second, the superior rib descended to fuse with the inferior one. The sternal part of these 3 specimens

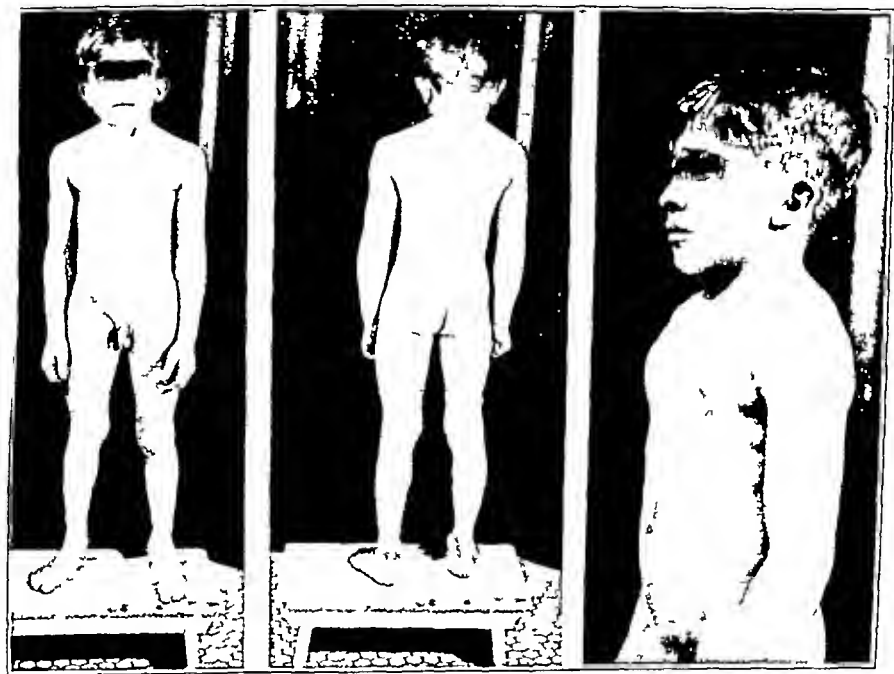


Fig. 1—Photograph taken May 1933. Front view showing head inclined to the right and right shoulder higher than the left.

Fig. 2—Photograph of back taken May 1933, showing dorsal scoliosis.

Fig. 3—Side view. Note bulging of right chest wall anteriorly.

showed no abnormality. In the remaining 3 specimens, the anomaly consisted "in an extension and more or less extended fusion of the neighboring borders of the ribs. In these cases we have seemingly a combination of a bicapital and bicaudal rib."

Meyer¹⁴ presents a specimen showing fusion of the second and third ribs of the right side throughout three quarters of their length. He mentions other cases cited in the literature from which one may infer that the anomaly occurs most often between a cervical and a first, and less often between the ribs next in order of their sequence becoming extremely rare below the fourth rib. Indeed, Meyer tells

of only one case of fusion below the fourth rib and that, supposedly in a seven month-old fetus which was said to have been in the possession of Hunauld

Ruppricht¹⁵ describes a fetus with union between the first and second ribs on the left side. He found 57 cases of rudimentary first ribs in the literature from 1820 to 1926. In 21 of the 57 cases, there was some kind of union to the neighboring rib. The union was bony, cartilaginous or otherwise. He found a higher ratio of union when cervical ribs were present. In only 12 of all cases found was there a continuation with the sternum. Where the first rib was beyond the rudimentary stage, he found 7 cases of union between the first and

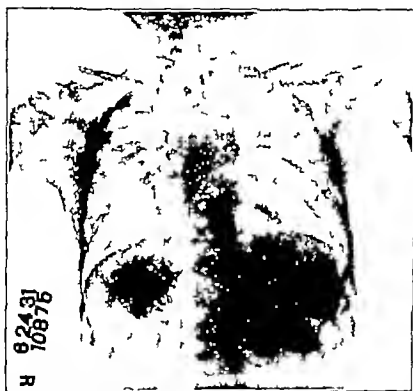


Fig. 4—Roentgenogram of chest. There is a fusion of five ribs into a sort of bony plate in the middorsal region of the left side.

On the right side, there is a union of two, three, or more ribs in the upper dorsal region and another union of two ribs below this.

second ribs. In cases with fully developed ribs he found 3 instances cited, and he himself chanced upon 2 other specimens in the Vienna Institute of Pathology.

Rees¹⁶ examined a six year-old girl who had a congenital scoliosis and found, among a number of bony defects, a union between the second and third ribs on the right side.

Gurney¹⁷ reported the case of a six year old girl who had what he describes as "ribs, many of them amalgamated at the back, two, and in one case three springing from the spine as one bone which separates into two (or three) about two inches from the middle line."

Hatch and Plume¹⁸ report a case of a seven year-old girl in whom

they found the sixth and seventh ribs fused for a short distance beyond their tubercles where the mass divided into four ribs varying in size

Sever⁸ presents a number of children with very gross deformities, among which I could make out 8 to 10 well-defined cases of fusion below the fourth rib. In 1 case there was fusion between the ninth and tenth ribs, and in at least 4 cases there was a fusion of three or more ribs. In Sever's cases the anomaly was about equally divided between the right and left sides



Fig 5 —Roentgenogram of the spine in the cervicodorsal region. Note the extensive spina bifida occulta and disorganization of the vertebral bodies.

SPINAL ANOMALIES

Spinal anomalies have been reviewed, in recent years, by a number of authors. Danforth,¹⁰ in an interesting paper on numerical variations in vertebrae, contends that the vertebra is in a sense plastic and this character of the vertebra is largely a function of its position. To this may be added Cushway and Maier's statement that examination of the individual vertebrae in their series revealed an approximation to the so-called average vertebra though none were found identical. "Each spine is characteristic of the individual, and he may be identified by a roentgenogram of the spine just as definitely as by a photograph of the face or by finger prints."¹¹

Willis,²⁰ in a very interesting article, concludes as follows

"1 The number of cervical vertebrae had been found practically constant not only in man but throughout the mammalian class

"2 The number of coccygeal segments is of negligible importance

"3 The vertebrae may be divided into two main groups, presacral and sacral

"4 Variation in the number of lumbar vertebrae is often coincident with, and compensated by, a reverse variation in the thoracic group. Likewise, at times, coincident with the lumbar variation a



Fig. 6—Roentgenogram of the lumbosacral region. There are six lumbar vertebrae. The sacrum is curved with convexity to the right. The first sacral segment shows a spina bifida occulta, a transverse process of the lumbar type on the right, and a lateral mass on the left.

reverse variation occurs in the number of sacral segments." With this in mind and also basing his opinion on the studies made by Todd²¹ on the comparative evolution of the vertebral column in the mammalia, he found a presacral numerical stability of 95.8 per cent.

Bohart²² says "Anomalies of the spine exist from statistics available in from 8 to 10 per cent of all persons examined." This, of course, includes all types of anomalies, both congenital and acquired.

A consideration of congenital anomalies of the spine entails a long list of malformations. For our present discussion, it will be necessary

to give only a very brief outline of the more obscure conditions. Among these we may consider

Spina bifida occulta

Variations in the body of the vertebra

Defect in the lamina

Congenital anomalies of the cervical spine

Numerical variations in the thoracolumbar region

Sacralization

Low lumbar, sacral, and coccygeal deformities

Spina bifida occulta is, by far, the most common congenital anomaly found in the spine. It may be found in any position of the vertebral column but more especially in the lower lumbar and sacral regions, the latter position being the most frequent site. Clinical manifestations do not necessarily accompany this deformity.

Variation in the formation of the vertebral body itself, is not common. The deformity may consist in a hemivertebra or otherwise malformed or displaced vertebra. When found in the thoracic region, one may expect some defect or abnormality in rib formation. Thus, in the cases cited by Sever and Rees, the thoracic spine showed this abnormality.

Incomplete union of the lamina is another deformity which is not common. Willis found 4.28 per cent of skeletons with this deformity. Cushway and Maier found only 2 cases in their series of roentgenograms in which the lamina was not united with the transverse process.

Congenital anomalies of the cervical spine are uncommon. Especially rare are those described under the obscure term of Klippel-Feil syndrome. This consists in a numerical variation in the cervical vertebrae with more or less complete fusion into one mass, accompanied, in some cases, with spina bifida or other anomalies.²³

Meisenbach²⁴ reports a case of total absence of the cervical spine in a girl ten years old.

Reference has already been made to numerical variations in the thoracic and lumbar regions. This anomaly is much more frequent in the lumbar region than it is in the thoracic region, but as Giles⁵ puts it, an absent twelfth rib may give one the impression that he is dealing with six lumbar vertebrae when the reverse may be the case. Giles found 50 cases with six lumbar vertebrae and 13 with four lumbar vertebrae. Cushway and Maier found 25 cases with six lumbar vertebrae, 6 with four lumbar vertebrae, and 5 with thirteen thoracic vertebrae. Each of the last 5 had thirteen ribs.

Sacralization, or articulation between the transverse process of the fifth lumbar vertebra and the sacrum, is the most common congenital anomaly of the spine next to spina bifida occulta. There seems to be a great divergence of opinion as to the importance of this condition.

and as to what does and what does not constitute true sacralization. It will be sufficient for our purpose to say that there are many different degrees of sacral transformation of the fifth lumbar vertebra, and that actual contact of bone, per se, may not give rise to symptoms. The bilateral occurrence is more frequent than the unilateral.

Coccygeal deformities are not painstakingly analyzed because most of them are of minor clinical significance and are usually considered along with sacral or other pelvic deformities.

Anomalies of the fifth lumbar are common, and anomalies of the low lumbar and sacrum are most common.

There may be what is sometimes termed "asacralization" or "lumbarization," in which the uppermost part of the sacrum takes on the characteristics of a lumbar vertebra.

Lastly there may be variation in the number of sacral segments or separation between them and accompanied by other associated malformations.

CASE REPORT

A white boy, five odd o half years old was brought to the clinic of the New York Nursery and Child's Hospital on June 24, 1931 because he was stunted in growth. The only previous history in connection with the deformity was an asymmetry in the chest wall which was first noticed when the child was two and a half years old.

The father and mother were both in their twenties and well. There was one other child, a boy aged seven years, who was apparently of normal physical development. The remainder of the family history was essentially negative.

Examination disclosed a boy 37 inches in height and weighing 29½ pounds. He did not appear to be very strong and talked in a weak almost piping voice. He had much dental caries. His head was inclined to the right. There were two small papillomas anterior to the tragus of his right ear. The crura anthellicis and the antihelix of this ear were sharply ridged. The right shoulder was higher than the left and a scoliosis was present. There was a bulging about the size of a plum in the midportion of the right chest wall anteriorly. There was a systolic murmur heard at the apex and at the pulmonary area but more pronounced at the latter.

A roentgenogram of the chest disclosed the uppermost ribs so closely grouped on both sides that it was difficult to distinguish their individual outlines. Somewhat below this, on the left side, there was fusion of at least five ribs into a sort of bony plate. On the right side, there was one union of two three or more ribs and another of two ribs directly below this. The ribs on this side did not seem to be in contact with the spine. The lowest four ribs on the left and the lowest three on the right appeared to be normal. The dorsal vertebrae, with the exception of the last three which were apparently normal, were of irregular shape and size and showed spina bifida occulta. There was also a scoliosis in this region with convexity to the right. The lumbar spine showed six vertebrae. The first sacral segment was asymmetrically developed and showed a lateral mass on the left side articulating with the ilium and a transverse process of the lumbar type on the right. There was marked pelvic asymmetry with deviation of the distal sacral segments to the left. There was a spina bifida occulta of the first sacral segment. The innominate bones were normal.

No abnormalities were found in the roentgenograms of the skull or long bones.

A few months after the first visit, the patient left for the country, and we did not hear from him until January, 1933

On Jan 23, 1933, his height was 41 $\frac{1}{4}$ inches and his weight 33 $\frac{3}{4}$ pounds. A Mantoux test with 0.02 milligrams of tuberculin resulted in a very strongly positive reaction. The mother later informed me that the child had frequently been in the company of a man who had since died of pulmonary tuberculosis. No definite signs could be found in his chest and he was referred to the x-ray department. A roentgenogram of the lung fields was taken on Mar 15, 1933.

The roentgenologist reported that the left hilum shadow appeared to be more dense and of nodular form. This was diagnosed as adenopathy of the left hilum.

The child is now in school and the report from the teacher states that he is studious, his work is satisfactory, he is always neat and clean, and socially very amiable. He is well liked by the other children in the class.

SUMMARY AND CONCLUSIONS

An outline of some of the more obscure congenital abnormalities of the ribs and spine is presented. To this is added the report of a boy having unusual deformities of this character.

The abnormalities discussed here can be correctly diagnosed only by x-ray or postmortem examination.

Cervical ribs, although not uncommon, are not as frequent as lumbar ribs.

Total absence, bifurcation, and fusion may be listed among the rare congenital rib conditions.

Spina bifida occulta is the most common finding and sacralization is next to it in frequency.

Numerical variations in the thoracolumbar region are not rare. Six lumbar vertebrae are found more often than four and both of these variations are more usual than thoracic variations.

Variations in the body of the vertebra and defect in the lamina itself, are found less frequently.

Absence of cervical vertebrae is rare. Reference is made to a case of total absence of the cervical spine.

The most common site for congenital spinal abnormalities is the lumbosacral region.

A report is given of a boy having a congenital scoliosis and showing a peculiar type of fusion of ribs. There are also extensive spina bifida occulta, irregularities in the vertebral bodies, and widespread sacral malformations.

REFERENCES

- 1 Steindler, A. Diseases and Deformities of the Spine and Thorax, St. Louis, 1929, The C. V. Mosby Co., p. 79.
- 2 White, J. D. Brit. J. Radiol. 2: 351, 1929.
- 3 Henderson, M. S. Am. J. Orth. Surg. 11: 408, 1914.
- 4 Cushway, B. C., and Maier, R. J. J. A. M. A. 92: 701, 1929.
- 5 Giles, R. G. Radiology 17: 1262, 1931.
- 6 Cumming, J. Brit. M. J. 1: 55, 1926.

- 7 Hrdlicka, A. A Contribution to the Osteology of Ribs, Proc. Ass'n Am. Anat., Baltimore 1900
- 8 Sever, J W Boston M & S J 188 799, 1922.
- 9 Bloomberg, M W Canad. M. A. J 16 807, 1926
- 10 Dennis C E M J Australia 2 603 1921
- 11 Ruppricht Ztschr f d. ges Anat. 91 402, 1920
- 12 Struthers J J Anat. & Physiol. 9 51 1875
- 13 Adams, J G Montreal M J 24 468 1896
- 14 Meyer, A W Anat. Rec 12 81 1917
- 15 Ruppricht W Anat. Anz. 65 131, 1923
- 16 Rees, H L Lancet 1 916, 1930
- 17 Gurney H. M. Newcastle N. J 3 100, 1923
18. Hatch H. S., and Plume C. A J A M. A 99 1254 1932.
- 19 Danforth, G. H. Am. J. Phys. Anthropol. 14 463, 1930
- 20 Willis, T A Am J Anat 32 93 1923
- 21 Todd T W Anat. Rec. 24 261, 1922
22. Bobart W H J A M. A 92 698 1920
- 23 Bauman, G L J A. M. A. 98 129 1932.
- 24 Meisenbach R O Am. J Orth. Surg 10 647 1912.

2349 TWENTY SIXTH STREET

VITAMIN D DEFICIENCY

TETANY IN INFANTS WITHOUT RICKETS

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FIVE infants with tetany, unassociated with roentgenologic evidence of rickets, are reported. That the tetany was dependent on a deficiency of ultraviolet radiant energy or vitamin D is evidenced by the prompt response to antirachitic therapy

The essential data are summarized in the table and the roentgenologic findings are illustrated in Fig 1 All infants received cow's milk in various dilutions during the hospital stay One (Case 2) received 2 grams of calcium chloride during the first day of treatment No calcium was given to any of the others



Fig 1—Roentgenograms of five infants with tetany unassociated with rickets

In all 5 infants treatment with antirachitic agents resulted in a prompt and complete disappearance of symptoms and a return of the serum calcium and the electrical reactions to normal

A number of other infants have been observed with tetany but without roentgenologic evidence of rickets (24 out of 125 cases) They are not presented here because they either left the hospital before cure was complete, or the results of specific treatment were obscured by the administration of calcium in fairly large amounts

That a deficiency of sunlight or vitamin D may be present without rickets is suggested by the studies of Daniels¹ who found a striking improvement in the calcium and phosphorus retentions in seemingly normal infants following the addition of cod liver oil to the diet or the irradiation of the milk in the feeding Swanson² noted a similar improvement in the phosphorus and calcium retentions in 2 infants with-

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TABLE I
THERAPEUTIC RESULTS WITH ANTHRACHITIC AGENTS IN FIVE INFANTS WITH TETANY AND WITHOUT RICKETS

CASE NUMBER	AGE MONTHS	SYMPTOMS	ANTHRACHITIC TREATMENT	BEFORE TREATMENT		AFTER TREATMENT		DURATION OF TREATMENT (DAYS)
				SERUM CALC. (MG PER CENT)	SERUM PHOS. (MG PER CENT)	SERUM CALC. (MG PER CENT)	SERUM PHOS. (MG PER CENT)	
1	6	Convulsions, laryngospasm active facial C.O.C. = 2.0*	Vigantol† Cod liver oil	6.5	4.3	10.2	6.7	7
2	1½	Convulsions C.O.C. = 4.0	Vigantol†	7.0	9.4	9.4	7.4	12
3	10	Laryngospasm	Cod liver oil	7.7	5.6	9.9	—	5
4	6	Convulsions, positive peroneal C.O.C. = 4.8*	Ultraviolet radiant energy	6.8	7.1	11.1	6.1	7
5	5	Active facial, myelogram laryngospasm	Vigantol†	9.7	8.2	10.6	6.3	18

C. O. C. Cathodal opening contraction in millimercs.

†Vigantol is an unanhydrous proprietary preparation of irradiated ergosterol of high antirachitic potency

‡Received 3 grams of calcium chloride during first day in hospital

out roentgenologic evidence of rickets and with normal values for the serum calcium and phosphorus, following the addition of cod liver oil to the diet

SUMMARY

1 Tetany in infants may occur without roentgenologic evidence of rickets

2 That this form of tetany is dependent on sunlight or vitamin D deficiency is evidenced by the prompt response to antirachitic therapy

REFERENCES

- 1 Daniels, A L, Stearns, G, and Hutton, M K Am J Dis Child 37 296, 1929
- 2 Swanson, W W Am J Dis. Child 43 10, 1932

132 EAST SEVENTY FIRST STREET

ADVANTAGES OF STRAINED SOLIDS IN THE EARLY MONTHS OF INFANCY

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DIFFERENCE of opinion still exists as to the best age at which to begin to feed cereals egg yolk, strained fruits, and strained vegetables to a well baby. Morse,¹ who represents the most conservative group, expressed the belief that cereal may be fed at the age of nine months, and advised a full diet at the age of one and a half to two years. Hess² and Brennemann,³ on the other hand, say that from five to eight months is the proper age for a full diet. Brennemann⁴ believes that introduction of solids into the infant's diet in comparatively early infancy (fifth and sixth months) is advantageous because the solids (1) contain vitamins, (2) have value in infant psychology, (3) are easily tolerated and (4) contain iron which is necessary. The earlier introduction of solids is not only advocated by most physicians but is practiced by most mothers.

The object of my study was to determine the best age at which to introduce solids into the well baby's diet, and to observe whatever advantages or disadvantages were presented by the early introduction of solids.

METHOD OF STUDY

A study was made of 231 infants who were observed in the Well Baby Clinic in the Roslindale District of the city of Boston in the years 1930 and 1931, and the first six months of 1932. This district contained for the most part, people of good social and hygienic surroundings, in moderate economic circumstances. The infants received medical care supported by nursing care from a group of well trained nurses connected with the clinic.

Solids were fed in the early months of infancy in such a way as to supplement the milk (breast or bottle) the infant got but not to complicate the feeding routine. This was done because too often mothers feed the infant as if he were a machine. For example the mother gives an infant one teaspoonful of carrots, two teaspoonfuls of spinach and seven ounces of milk. In this way she pays no attention to the natural power of selection of the infant, although the appetite of an infant will vary from day to day and from meal to meal. I believe that an infant should be allowed some choice as to the amount and kind of food which he receives. This has scientific support, for in 1915 Edwards⁵ allowed a group of hogs to select whatever they wished and as much as they wished from an assorted variety of basic food stuffs. The amount and type of food actually eaten by the hogs was found best for their nutrition and development. Cowgill,⁷ in 1928, showed that dogs also are able

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to choose for themselves the optimum amounts of a complete food Davis,⁸ in 1927 and in 1928, showed that this power of selection was correct in newly weaned normal, anemic, and rachitic infants

This natural power of selection of food by the infant was utilized in this study At all times the infant was allowed to take as much food as it wished Bottle fed infants were prescribed formulas containing milk, water, and sugar (Mead's dextrin maltose, Karo syrup, milk sugar, or cane sugar) Three teaspoonfuls of cod liver oil and three ounces of orange juice daily were prescribed (summer or winter) for every infant Cod liver oil, however, was omitted during a hot spell or whenever the infant's appetite was impaired The infants were seen once a week or once in two weeks, and the formula was changed as the indication arose

When solids, such as fine wheat or barley cereal, were introduced into the infant's diet, the mother was instructed to teach the infant to swallow them Ordinarily an infant from two to four months old easily learned to swallow the well cooked and strained cereal that was softened with milk Occasionally, it took two weeks (twenty eight attempts) to teach a determined infant six to eight months of age to swallow solids When the infant learned to take cereal, the mother was told to give it all it wished As more cereal was taken, less sugar was included in the formula The cereal was given at 10 A M and 6 P M and was followed by bottle or breast After the infant learned to take cereal well, Zwiebach, toast, egg yolk (cooked ten minutes), strained fruits, and strained vegetables were added to the diet One teaspoonful of a new food was tried at one feeding and old foods could be mixed if desired After the solids were eaten, the infant was allowed to take as much milk as it wanted The following rules were emphasized (1) boil everything the infant eats, (2) start only one new food a day, one teaspoonful at first, gradually increasing the amount, (3) give solids at the beginning of the feeding, (4) let the infant eat as much as it wants, (5) never force the infant to eat, and (6) if the infant refuses food, give water and orange juice until the next feeding time, and repeat this procedure until it is hungry

The full diet of solids was as follows (1) at 6 A M, milk (formula, whole milk, or breast milk), (2) at 8 A M, cod liver oil and orange juice, (3) at 10 A M, cereal or Zwiebach, and milk, (4) at 2 P M, (a) broth or beef juice, (b) egg yolk, (c) potato, rice, or macaroni, (d) strained green vegetable (two of the following spinach, peas, string beans, stewed celery, carrots, squash, stewed tomatoes), and (e) milk, (5) at 6 P M, (a) cereal or Zwiebach, (b) apple sauce, prune pulp, or strained apricots, and (c) milk, (6) at 10 P M, milk if the infant is awake During the eighth, ninth, and tenth months, simple desserts, such as Jello, junket, and sherbet, prepared cereals, and strained meats were added to the diet

RESULTS

The 231 infants that were fed in the manner described were divided into four groups according to the age at which solids were first given Group I, during the second and third months, 38 infants, Group II,

TABLE I
WEIGHT IN RELATION TO SITTING HEIGHT

	NUMBER OF INFANTS	PER CENT WITH WEIGHT WITH IN THE CALCULATED NORMAL WEIGHT RANGE BASED ON SITTING HEIGHT
Group I	15	87
Group II	11	82

during the fourth month, 53 infants Group III during the fifth and sixth months, 97 infants and Group IV, during the seventh eighth ninth and tenth months 43 infants Each group was studied for (1) nutrition and development (2) effect on the gastrointestinal tract and (3) effect on food habits

TABLE II
WEIGHT (IN POUNDS) ACCORDING TO AGE

	BIRTH	2 MO	4 MO	6 MO	8 MO.	10 MO	1 YR.
Group I	7.7	10.6	14.5	17.5	20.0	21.7	23.3
Group II	7.5	10.3	14.0	16.8	19.2	21.1	22.7
Group III	7.6	10.3	13.5	16.3	19.1	20.6	22.0
Group IV	7.7	10.7	14.0	16.6	18.7	20.5	22.4

Nutrition and Development—Weight was regarded not only as a measure of the infant's nutrition but also in relation to the skeletal structure. For a number of infants observed in Groups I and II it was possible to record the so-called normal weight as calculated from the sitting height of the infant,¹⁰ and to compare this normal weight with the actual weight of the infant. Thus, if certain groups show an unusual

TABLE III
DEVELOPMENT

	NUMBER OF INFANTS	DENTITION MONTHS	TIME OF WALKING MONTHS
Group I	32	6.5	12.1
Group II	31	6.6	12.5
Group III	70	7.2	12.3
Group IV	27	7.5	13.4

gain in weight, this gain in weight is desirable when it approximates the normal weight as calculated from the sitting height

Thirteen of the 15 infants in Group I and 9 of the 11 infants in Group II, whose calculated normal weights were recorded had actual weights within calculated normal limits (10 per cent) as shown in Table I.

In Groups I and II (solids given early) the yearly average gain in weight was respectively 0.9 and 0.7 pound greater than the weight gained in a year by infants of corresponding birth weight in Groups III and IV (solids given later). The weight of each group is given in Table II.

Dentition occurred earlier in the groups in which solids were introduced into the diet early as shown in Table III. Furthermore the age at dentition in Group I was one whole month earlier than in Group IV.

There was also a definite relationship between early walking and early feeding of solids as shown in Table III. The infants in Group I started to walk at an average of 12.1 months, while the infants in Group IV started to walk at an average of 13.4 months.

Effect on the Gastrointestinal Tract—The solids were easily digested in all the groups, which included 166 infants. In the groups in which solids were given early there were fewer gastrointestinal disturbances associated with extraintestinal causes, and far fewer disturbances directly related to the gastrointestinal tract.

The first time strained vegetables were given, whether early or late, most of them were observed in the stool without much digestion, and they colored the stool. Carrots, beets, tomatoes, and string beans were well digested the second or third time they were eaten. Spinach required four to five attempts before it was digested to any appreciable degree.

TABLE IV
EFFECT ON THE GASTROINTESTINAL TRACT

	NUMBER OF INFANTS	PRESENCE OF CONSTIPATION		PRESENCE OF GASTRIC DISTURBANCES	GASTRIC DISTURBANCES WITHOUT EXTRA INTESTINAL CAUSES
		BEFORE DIET ADDED	AFTER DIET ADDED		
Group I	28	38.6%	11.5%	28.5%	3.5%
Group II	37	37.9%	10.8%	29.7%	5.4%
Group III	73	41.1%	12.3%	45.7%	18.5%
Group IV	28	73.5%	32.1%	32.1%	17.9%

TABLE V
EFFECT ON FOOD HABITS

	NUMBER OF INFANTS	PRESENCE OF FAULTY HABITS	ENJOYMENT OF FOOD	PRESENCE OF FOOD DISLIKES
Group I	26	69.2%	93.0%	42.7%
Group II	37	43.3%	89.2%	35.1%
Group III	71	52.1%	77.0%	50.7%
Group IV	27	63.0%	77.7%	51.8%

In a few cases in which a wide variety of new cereals, vegetables, and fruits were tried within a few days an interesting syndrome developed. The infant took the foods well, was active, slept well, and had a bowel movement once or twice a day, which was brownish or the same color as the vegetables. There was no gain in weight and sometimes even a loss of one to two ounces for a week, but after this the gain was within normal limits.

When cereal was added to the diet, the character of the stool changed very little. In some cases the stool became softer and occurred twice a day instead of once. The addition of egg yolk to the diet gave the stool a golden brown color. In a few cases vomiting occurred, but this was due to egg-idiosyncrasy. When a bowel movement is soft, semisolid, ranging in color from yellow to brown, having very little odor, and occurring regularly once or twice a day, it is safe, as a rule, to say that the type of food ingested is proper.

The groups in which vegetables were given early showed a definite decrease in chronic constipation (Table IV). Constipation was present in about 40 per cent of the cases but the earlier a diet containing solids was given the fewer the cases of chronic constipation. Although 70 per cent of the constipated infants of less than seven months of age were relieved by the addition of solids only 40 per cent of the infants from seven to ten months of age were so relieved.

Effect on Food Habits—Each group was studied as follows: (1) presence of faulty habits such as temper tantrums, crying to be picked up, wishing own way, and difficulty in sleeping; (2) enjoyment of food; and (3) definite dislike of any food or foods.

The results (Table V) show that the groups fed solids early had better food habits and fewer food dislikes than those fed solids later. Group I had 7 per cent more food dislikes than Group II, but in the presence of 26 per cent more faulty habits in Group I the result was not so striking since there is a tendency for food dislikes among infants with faulty habits.

Explanation of Results—A sufficient amount of vitamins and minerals is necessary for proper nutrition and development of an infant. Frequently breast milk or formula milk does not fully supply this need even with the addition of average amounts of cod liver oil and orange juice. Apparently the reason why a full diet of solids is desirable is not that breast or bottle food does not contain the vitamins but rather that they are often contained in insufficient quantity.

A full diet of strained solid foods supplies an abundance of vitamins A, B, C, and D. Such a diet gives an oversupply of vitamin A which may be stored in the body and used when needed, thus increasing vigor and resistance to disease.¹¹ Vitamin B is often deficient in either human or cow's milk.^{12, 13, 14, 15, 16} The amount of vitamin C necessary to prevent scurvy is only a fraction of the optimum amount needed. Vitamin D is particularly required in the metabolism of phosphorus and calcium.¹⁷ Wilson¹⁸ made roentgenographic examination of infants who had received cod liver oil and found rachitic changes in the bones of 97 per cent of those examined, probably due to an inadequate amount of cod liver oil. For Hess¹⁹ believes that at least 15 cc. of cod liver oil daily are necessary to supply the vitamin D content necessary to prevent rachitic changes in the average infant. The diet of strained vegetables possesses all of these vitamins in adequate quantities to effect proper development and nutrition for a normal infant.

Although cow's milk and human milk contain all of the minerals necessary for development, both are conspicuously deficient in iron. Rapid growth and increased production of blood in the newborn infant²⁰

depend upon a reserve of iron deposited in the liver. The liver of the newborn animal contains at least five times as much iron as is found in the liver of the full-grown animal.

Since milk is deficient in iron, one might expect the hemoglobin content of blood to be much higher at birth than in later infancy. Williamson,²¹ in 1916, proved this to be true. He showed that newborn infants average 23.2 gm of hemoglobin per 100 cc of blood, that by the end of the second month the hemoglobin drops to 18.3 gm, that by the end of the fifth month it drops to 13.7 gm, and that the drop continues until at the end of the twelfth month the hemoglobin is 12.5 gm per 100 cc of blood.

The German investigators, Schwartz, Baer, and Weiser,²² could not find, by histologic examination, any iron in the infant's liver or spleen after the fifth month. This means that all the iron stored in the newborn infant's liver is completely used up before the sixth month, and there after the infant is entirely dependent for iron on the intake of food. Mayers²³ suggested that the drop in hemoglobin during the first year of the infant's life is a nutritional anemia, resulting from faulty feeding.

The amount of iron required daily by an infant has not been determined. Morse²⁴ has expressed the belief that 0.5 mg of iron daily is sufficient for the first six months, and that 1.5 mg of iron daily is necessary for the second six months. Larger amounts of iron, however, could well be used, for there is a definite relationship, within certain limits, between intake of iron and increase in hemoglobin. The addition of strained solid foods in the early months of infancy supplies a diet rich in iron and helps to prevent the nutritional anemia frequently present.

The infants in my series showed definite ability to digest strained solids, even in the early months of infancy (second and third months). This easy digestibility may be due to the recent great improvement in the manufacture of strained fruits and vegetables. Caldwell,²⁵ in his series of 60 infants, showed that strained vegetables were tolerated and digested at as early an age as six weeks. Introduction of cereal in the second month was not a radical step, for cereal is used to feed infants with pyloric spasm even during the early weeks of life. Strained vegetables when first fed the infant passed through the intestinal tract without any appreciable digestion. After two or three attempts the digestion of the strained vegetable was much improved. Apparently vegetables require certain digestive ferments to digest them. The production of these ferments, originally absent, seems to be stimulated by the ingestion of vegetables, with function soon following.

The "stationary weight" syndrome (failure to gain weight without other clinical evidence) followed the rapid introduction of many new strained solids. Apparently this was due to the metabolic change while the digestive ferments were being produced.

Constipation was present in about 4 of every 10 infants in the group of 166 studied, but the earlier the solids were given the fewer the cases of chronic constipation. Although 70 per cent of the constipated infants of less than seven months of age were relieved by the addition of solids, only 40 per cent of the infants from seven to ten months of age were so relieved. The reason for this beneficial effect in the early months is apparent. Too small an amount of solids is an important cause for constipation. When this condition exists the mother gives the infant a laxative or a cathartic. Repeated administration of these results in maladjustment of bowel mechanism so that the bowel muscles do not function until stimulated by a laxative and the result is a sluggish bowel (atonic constipation). When solids are introduced early in infancy there is a sufficient amount of total solids in the infant's diet thus eliminating the cause of atonic constipation.

The study showed that the groups fed solids in early infancy had better food habits and fewer food dislikes than the groups fed solids in later infancy. The explanation for this is that the longer the infant is on breast or bottle (without solids) the more accustomed it becomes to the milk (milk habit) and the harder it is for the infant to develop a liking for solids. The early feeding of solids stimulates a desire for a variety of foods and greatly aids in improving the infant's food habits.

CONCLUSIONS

A full diet of strained solids including strained vegetables given during the second and third months of infancy produces better nutrition and better food and bowel habits because (1) it contains adequate amounts of vitamins A, B, C and D (2) it contains iron that is needed to prevent nutritional anemia (3) it provides bulk to the stool, eliminating an important cause for constipation in infants and (4) it accustoms the infant to solid food early in life thus improving its food habits.

I wish to thank the following persons for their cooperation: Francis X. Mahoney, M.D., Commissioner of Health, City of Boston, Charles F. Wilinsky, M.D., Director of Well Baby Clinics, City of Boston, and Hazel Wedgewood, R. N., Director of Nurses, Health Department, City of Boston.

REFERENCES

1. Morse, J. L. *Clinical Pediatrics*, Philadelphia, 1926 W. B. Saunders Co.
2. Hess, J. H. *Feeding and Nutritional Disorders in Infancy and Childhood*, Philadelphia 1928, F. A. Davis Co.
3. Brennemann, Joseph. *Artificial Feeding of Infants*, In *Abts Pediatrics* Vol. II chap. 23 1923 p. 705
4. Brennemann, Joseph. *Artificial Feeding of Infants*, In *Abts Pediatrics*, Vol. II chap. 23, 1923 pp. 702-704
5. Wilinsky, C. F. *Boston M. & S. J.* 104 491 1926
6. Edward. *Proc. Iowa Acad. Sc.* 22 375 1915
7. Cowgill, G. R. *Am. J. Physiol.* 85 45 1928
8. Davis, Clara M. *J. Am. Dent. A.* 14 1110, 1927
9. Davis, Clara M. *Am. J. Dis. Child.* 36 651 1929
10. Glazier M. M. *New England J. Med.* 201 888, 1929
11. Sherman H. C. *Chemistry of Food and Nutrition* ed. 3 New York, Macmillan Co., pp. 457-459

- 12 Macy, I G, Outhouse, Juha, Graham, Alice, and Long, M L J Biol Chem
73 189, 1927
- 13 Hoobler, B R J A M A 91 307, 1928
- 14 Hoobler, B R J A. M A 96 675, 1931
- 15 Bloxson, A P Am J Dis Child 37 1161, 1929
- 16 Waring, J I Am J Dis Child 38 52, 1929
- 17 Sherman, H C, and Stiebeling, H K Proc Soc Exper Biol & Med 27
663, 1930
- 18 Wilson Quoted by Howe, P R J Am Dent A 1673 1677, September, 1928
- 19 Hess and his collaborators Editorial J A M A 99 565, 1932
- 20 Bunge, C Physiological and Pathological Chemistry (Translation) 1902,
p 377
- 21 Wilhamson, C S Arch Int Med 18 505, 1916
- 22 Schwartz, P, Baer R, and Weiser, J Ztschr f Kinderh 37 167, 1924
- 23 Mayers, L H Arch Int Med 30 478 1922
- 24 Morse, J L Clinical Pediatrics, Philadelphia, 1926, W B Saunders Co
- 25 Caldwell, G W J PEDIAT 1 749, 1932

A CRITICAL CLINICAL STUDY OF VARIOUS INFANT FOODS

III FRESH WHOLE MILK MODIFICATION WITHOUT FAT DEFICIENCY

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IN A SERIES of articles of which this is the third we have examined clinically various infant foods. This clinical study comprises a total of 259 cases, 149 of which were fed on whole milk modified by the method herein described and 100 of which were fed whole milk modified by a maltose and dextrin carbohydrate used as a control.

The successful artificial feeding of infants consists in the adaptation of cow's milk in such a manner that the two following conditions are fulfilled.

1 The nutritional needs must be supplied by the mixture as completely as possible.

2 The formula must be adjusted so that it will be successfully tolerated by the digestive system and produce favorable digestive reactions.

The history of infant feeding is characterized by innumerable attempts to meet these conditions in a satisfactory manner. The standards for the nutritional needs have become fairly definitely fixed. It is obvious that the infant's needs are met by a formal amount of human milk of average composition. Based on a study of this natural supply and confirmed by records of successful artificial feeding, it has been established that the average infant requires about 50 calories per pound of body weight daily conveyed in a fluid volume of about two and one-half ounces, so that each ounce of food is valued at about 20 calories. This is the caloric concentration of human milk and may be assumed to be the correct physiologic standard. These calories, of course, are provided by fat, protein and carbohydrate. Protein cannot be synthesized in the body and the needed amount of protein of proper quality must be supplied in the food given. Human milk provides in each two and one-half ounces (50 calorie portion) about 10 gram of protein and this amount meets the needs of the infant per pound daily. The fact has been established that cow's milk protein is different in quality from that of human milk and, to compensate for this difference, it is necessary to give the infant 15 grams of cow's milk protein to be equivalent in nutritional value to the 10 gram taken in human milk. This amount of cow's milk protein is contained in 15 ounces of whole cow's milk and is the accepted basis for the minimum cow's milk need per pound for the artificially fed infant. To compound an adequate cow's milk formula for the infant it is therefore necessary to give daily,

for each pound of body weight, 15 ounces of cow's milk diluted to two and one-half ounces with water and so reinforced by food additions that this volume will convey 50 calories. One and one-half ounces of cow's milk conveys 30 calories, so that 20 calories must be provided by the food additions. These additional calories can theoretically be supplied by fat, carbohydrate, or protein, or any combination of these elements if calories only are to be considered, since they are fundamentally energy supplies. However, since digestive conditions must also be taken into consideration, the distribution of these calories among the different food elements is of utmost importance. It is natural to turn at this point to human milk as a guide. Human milk contains over 3 per cent of fat and about 7 per cent of sugar, but less protein than this diluted cow's milk. There seems to be little indication, therefore, for adding any extra protein to the mixture. Moreover, cow's milk protein in excess of the needs is not advantageous or even desirable. Protein requires more energy expenditure for the process of digestion and the excretion of end-products, and an excess of protein in the food mixture affects digestive conditions in a manner which often proves undesirable, leading to constipation, putrefactive conditions, and high mineral excretion. On the other hand, it seems of great significance that nature provides the infant with such a high proportion of fat. Most pediatricians have always recognized this significance. Fat is of great importance as a source of the fat soluble vitamins. Fat aids the digestion of protein and stimulates the proper assimilation of minerals, especially calcium. It also provides over twice as many calories per gram as does either carbohydrate or protein. Fat benefits digestion, and tends to control excessive fermentation and to keep the intestinal reactions well balanced, thus producing normal stools. Accordingly, many attempts have been made to reinforce the fat content of cow's milk formulas so that it will compare favorably with that in human milk. These attempts were carried out by using top milk mixtures of such strength that the proportion of fat after dilution was similar to that in human milk, the remaining caloric deficiency being made up by carbohydrate. It was found that many infants could not digest such a mixture successfully. This failure was undoubtedly due to the fact that cow's milk fat is less easily digested by the infant than the fat of human milk, chiefly because the fat of cow's milk occurs in large tough globules. Accordingly, the attempt to supply any considerable part of the needed additional calories in whole milk dilutions in the form of fat was largely abandoned, and the general procedure in artificial feeding was to provide rather more than the minimum amount of whole cow's milk and to make up the caloric deficiency by carbohydrate alone, being perforce satisfied to give only the amount of fat conveyed by the amount of whole milk used. Since infants can usually tolerate more fresh cow's milk fat than that supplied by the minimum need for cow's milk, as determined by the protein requirement, this procedure permitted the use of formu-

las which supplied from one half to three-quarters as much fat as would be supplied by human milk. Such mixtures were found to be quite generally tolerated by average healthy infants. It was always recognized that the proportions of fat, carbohydrate, and protein differed markedly from Nature's guide, human milk, and that the mixture was, therefore, not ideal, but, since a consideration of the digestive tolerance is equally as important as the provision of a theoretically correct mixture of ingredients this compromise was accepted as necessary.

In the meanwhile, the advance of scientific knowledge presented increasing evidence of the beneficial effects of generous fat in the diet. In the meanwhile, also the advance of scientific knowledge has shown the way to meet this fat need without disturbing digestion. It is well known that the difficulty which the infant demonstrates in digesting raw cow's milk fat tends to disappear when the milk is processed in any way. Concentrated milks have long been recognized to be much more readily digested than fresh milk. The introduction and increasing use of dried milk and dried milk products have proved that infants have little difficulty in digesting the milk fat of milk which has been dried especially if homogenization has been introduced into the process of manufacture. Definite proof of this is the marked success achieved in the use of several dried modified milks now generally in use. Innumerable physicians have found that infants can successfully tolerate and thrive exceptionally well on feedings containing 3 to 35 per cent of processed milk fat.

The inference is obvious. If enough fresh raw cow's milk fat cannot be successfully added to a fresh milk dilution so that the mixture simulates human milk in proportions of fat, carbohydrate, and protein, and if infants can successfully tolerate increased amounts of processed milk fat the addition of processed milk fat rather than fresh milk fat is certainly indicated.

A milk modifier which embraces these principles has therefore been devised. Instead of consisting as do the commonly used milk modifiers, of carbohydrate alone, this modifier consists of a mixture of processed cow's milk fat, mixed easily digested carbohydrates, a small amount of protein, and a significant amount of mineral salts, especially iron. By using this modifier, it becomes possible to add to the desired minimum of fresh cow's milk the needed additional calories *partly as fat* and partly as carbohydrate. The final mixture therefore, approaches more nearly to the proportion of food ingredients found in human milk than has ever been possible to achieve by the use of usual modifiers but does not overstep the infant's fat tolerance, since the fat addition is the easily digested processed homogenized milk fat.

It was shown earlier that the basis of proper feeding for the artificially fed infant was a minimum of 1.5 ounces of cow's milk made up to a volume of 2.5 ounces with water. To this there was to be added enough additional food to provide 20 more calories, making a total of 50 calories for

each 25 ounces of mixture. If carbohydrate alone is added to supply this deficiency, it is necessary to add about 5 grams of carbohydrate. The resulting percentage composition of such a formula would be

Formula A—Cow's milk, 15 ounces, water, 1 ounce, carbohydrate, 5 grams

Fat	20%
Carbohydrate	87%
Protein	18%

These proportions are vastly different from those found in human milk, and the mixture is so high in carbohydrate that some infants would show evidence of the carbohydrate tolerance being exceeded. In many instances, therefore, the added calories are supplied partly by increasing the amount of cow's milk and partly by added carbohydrate, as for example

Formula B—Minimum milk, 15 ounce, added milk, $\frac{1}{2}$ ounce, water, $\frac{1}{2}$ ounce, carbohydrate, 25 grams

Fat	28%
Carbohydrate	67%
Protein	25%

Such formulas are usually well tolerated, although some infants find difficulty in handling so much fresh milk fat and the balance of food elements is far from that in human milk.

With this new modifier, 4 grams are added to the basic mixture of 15 ounces of cow's milk with 1 ounce of water. The resulting formula has a percentage composition as follows:

Formula C—1 ounce of whole milk, 1 ounce of water, 4 grams modifier

Fat	31%
Carbohydrate	59%
Protein	21%

The mixture approaches the composition of human milk, the fat being very similar in amount. The protein is necessarily higher and the carbohydrate is therefore lower in proportion. Since only 60 per cent of the fat supplied in such a mixture is raw cow's milk fat, while 40 per cent is processed fat, it is possible for the infant to take this relatively high proportion of fat without digestive disturbance. The digestive conditions on such a feeding should approach those of infants on breast milk feeding.

The relation of the food elements to each other in the different formulas explained above is readily seen in Table I, which gives the proportions of fat, carbohydrate, and protein in the total solids of the formulas.

TABLE I

PER CENT OF TOTAL SOLIDS	HUMAN MILK	FORMULA A (1.5 OZ. MILK, 1 OZ. WATER 5 GR. CARBO- HYDRATE)	FORMULA B (2.0 OZ. MILK 0.5 OZ. WATER, 2.5 GR. CARBO- HYDRATE)	FORMULA C (1.5 OZ. MILK, 1 OZ. WATER, 4 GR. MODI- FIER USED IN THIS STUDY)
Fat	30.5	10.0	23.4	28.0
Carbohydrate	56.5	69.0	56.8	53.2
Protein	13.0	14.4	20.8	18.8

In addition to providing the infant with sufficient calories, water, protein, fat and carbohydrate it is necessary to consider carefully the supply of minerals and vitamins. Any formula which provides enough cow's milk to meet the protein needs adequately conveys milk salts in amounts greater than those provided by human milk. Cow's milk contains three and one-half times as much mineral matter as does human milk with the individual mineral constituents in approximately the same relation to the total ash, iron being the only marked exception. Accordingly, a dilution of 15 ounces of cow's milk to 25 ounces with water will still provide over twice as much mineral matter as 25 oz. of human milk. The use of this modifier further augments this supply because of the appreciable amount of milk salts contained in it. The only specific mineral substance whose content in cow's milk compares unfavorably with that in human milk is iron. Even in human milk the amount of iron provided for the infant is questionably adequate, while cow's milk is notably deficient in this element. Accordingly this modifier has been reinforced in iron content so that a formula in which it is used contains three times as much iron as a corresponding one made with the ordinarily used carbohydrates.

Whole cow's milk provides a vitamin supply fairly comparable to that in human milk. Dilution of course diminishes this supply especially in regard to the fat-soluble vitamins A and D. This modifier by rendering the net fat content of the formula similar to that of human milk tends to compensate for this loss of dilution insuring a vitamin supply similar to that of whole cow's milk. The supply of water-soluble vitamin B in a formula using this modifier exceeds that of ordinary milk formulas. This is due to the fact that it is made partly from malted whole wheat grain by a process which retains to a large extent the original vitamins of the grain. Whole wheat is known to be one of the richest sources of vitamin B. This additional supply of Vitamin B is of undoubted benefit to the infant. Vitamin B stimulates appetite and growth. Vitamin C as always in infant feeding, must be provided by dietary additions of fruit juice.

In brief this modifier used with dilutions of whole cow's milk makes it possible to offer to the infant, formulas which contain generous protein mineral salts and vitamins, with increased supply of iron and vitamin B and with a generous supply of easily digested fat similar

each 25 ounces of mixture. If carbohydrate alone is added to supply this deficiency, it is necessary to add about 5 grams of carbohydrate. The resulting percentage composition of such a formula would be

Formula A—Cow's milk, 15 ounces, water, 1 ounce, carbohydrate, 5 grams

Fat	20%
Carbohydrate	87%
Protein	18%

These proportions are vastly different from those found in human milk, and the mixture is so high in carbohydrate that some infants would show evidence of the carbohydrate tolerance being exceeded. In many instances, therefore, the added calories are supplied partly by increasing the amount of cow's milk and partly by added carbohydrate, as for example

Formula B—Minimum milk, 15 ounce, added milk, $\frac{1}{2}$ ounce, water, $\frac{1}{2}$ ounce, carbohydrate, 25 grams

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The relation of the food elements to each other in the different formulas explained above is readily seen in Table I, which gives the proportions of fat, carbohydrate, and protein in the total solids of the formulas.

The mineral elements in the ash of the modifier are approximately as follows

Potassium	0.296%
Sodium	0.596%
Calcium	0.210%
Magnesium	0.079%
Iron	0.0036%
Sulphur	0.140%
Phosphorus	0.160%
Chlorine	0.135%

The caloric value of the dry powder is 5 calories per gram or 150 calories per ounce, or expressed in spoonfuls

- 1 level teaspoonful of modifier dry, or 1.7 grams—8.5 cal
- 1 level tablespoonful of modifier dry, or 5 grams—25 cal
- 1 ounce by weight—18 level teaspoonfuls or 6 level tablespoonfuls.

The curd tension of various formulas made with milk, water and modifier used in this study has varied from 3.9 to 12.7

CLINICAL STUDY

The clinical study of this modifier was divided into two groups the first group consisting of 99 cases using milk water and added modifier. The fat infants over four months of age received from 40 to 45 calories per pound body weight, the average infants under four months of age and moderately thin infants of any age were given from 50 to 55 calories per pound body weight and babies underweight for age were given 60 to 65 calories per pound body weight. In the 99 cases in this group the modifier was added as a carbohydrate would be added the babies under ten pounds in weight getting 120 calories per day in the form of modifier and the babies over ten pounds in weight getting 180 calories. Table II shows the results of this group.

TABLE II

Number of infants on modifier	99
Youngest infant put on modifier	2.0 weeks of age
Average age of infants put on modifier	2.5 months
Minimum length of time on modifier	6.0 weeks
Average length of time on modifier	16.6 weeks
Maximum length of time on modifier	7.5 months
Average weekly gain per infant	5.21 ounces
Number of digestive disturbances	7 (6.98%)

Of the seven digestive disorders above mentioned one was in the form of anorexia and six of diarrhea two of which had an associated anorexia.

As the caloric value of a tablespoonful of this modifier is 25, 8 to 9 tablespoonfuls per day were eventually given to all infants. The one case of anorexia occurred when the modifier was increased to 9

tablespoonfuls and corrected when this was reduced to 7. The cases of diarrhea were all of the fermentative type, having 5 to 7 yellow to green semisolid stools a day. Five of the 6 cases occurred when the formula contained 9 tablespoonfuls of the modifier and the remaining one when 8 were used. All the stools returned to normal in from three to five days by the simple removal of the modifier.

Each of the gastrointestinal upsets was very carefully studied. It occurred to us that it would be possible to reduce the percentage of fresh cow's milk fat and increase the processed fat by a readjustment of the formulas. With this in view, a series of formulas (Table III) were calculated. These show that by a reduction of the amount of fresh cow's milk and by an increase in the amount of the modifier, the percentage of processed fat could be increased. Fifty infants were fed according to the formulas in Table III. The number of gastrointestinal upsets were, however, approximately the same in both groups. Nevertheless, the average gain in weight was considerably higher in the second group, and we believe that the best results with this modifier will be obtained by following the method as outlined in Table III.

The difference in feeding in this manner from that used in the first group is best explained by sample cases.

Baby J. D., aged three months, weight 12 pounds. Assuming that this baby requires 50 calories per pound body weight, the total calorie requirement would be 600.

Formula of First Group

Milk	21 ounces
Water	10 ounces
Modifier	11½ ounces (approximately 8 table- spoonfuls)

Formula of Second Group

Milk	19 ounces
Water	14 ounces
Modifier	10 tablespoonfuls

In a five-and-a-half-month-old baby, weighing 14½ pounds, requiring 725 calories a day, the difference in methods of feeding is still more clearly brought out.

Formula of First Group

Milk	27 ounces
Water	10 ounces
Modifier	8 or 9 tablespoonfuls

Formula of Second Group

Milk	23 ounces
Water	12 ounces
Modifier	11½ tablespoonfuls

TABLE III

AGE	FEEDING TABLE			PROPER MILK ALLOWANCE				PERCENTAGE COMPOSITION BY WEIGHT					PROPORTIONS OF FAT	
	WEIGHT (LB.)	NUMBER OF FEEDINGS	AMOUNT EACH FEEDING (OZ.)	TOTAL 24 HOUR VOLUME (OZ.)	WHOLE MILK (OZ.)	WATER (OZ.)	MODIFIER	FAT	CARBOHYDRATE	PROTEIN	TOTAL CALORIES	APPROXIMATE CALORIES PER OZ. VOL.	RAW FAT (PER CENT)	HOMOGENIZED AND PROCESSED FAT (PER CENT)
1 da.	6-8	4	1	4	1	3	2 tsp	14	27	0.9	37	9	01	30
2 da.	6-8	7	1	6	2	4	4 tsp	18	36	1.2	43	1	02	39
3-4 da.	6-8	7	1½	10½	3½	7	7 tsp	18	36	1.2	133	17	02	39
5-7 da.	6-8	7	1½	10½	4½	6	8 tsp	24	48	1.6	105	16	6	39
2 wk.	7-9	7	2½	17½	8½	0	4½ tbsp	25	40	1.7	282	17	66	34
3 wk.	7-9	7	3	21	11	10	0 tbsp	27	53	1.9	370	18	06	34
4 wk.	8-10	7	3½	24½	14	10½	7 tbsp	29	55	2.0	455	18½	08	32
2 mo.	8-11	7	4	28	16	11	8 tbsp	30	57	2.1	620	19½	08	32
3 mo.	11-13	7	5	35	20	14	10 tbsp	30	57	2.1	650	18½	09	32
4 mo.	12-14	6	0	36	21	14	12 tbsp	32	0	2.1	695	10	67	33
5 mo.	14-16	5	0	35*	22	12	12 tbsp	32	01	2.3	720	20	68	32
6 mo.	15-17	5	7½	37½	23	13½	12 tbsp	32	00	2.3	760	20	67	33
7 mo.	16-18	5	8	40	24	14	12 tbsp	32	00	2.3	900	20	69	31
8 mo.	17-19	5	8	40*	27	12	12 tbsp	33	00	2.4	810	20	72	28
9 mo.	18-21	5	8	40	29	10	10 tbsp	34	60	2.5	930	21	75	24

*The amount of modifier added increases the volume of daily formula by about 1 oz.

This table allows at least 15 gr protein per lb. body wt. At no time until the eighth month is the raw fat as high as 10 per cent of the total.

The eighth and ninth month formulas pave the way to whole milk.

TABLE IV

Number of babies on modifier	50
Youngest infant put on modifier	135 months
Average length of time on modifier	18 weeks
Maximum length of time on modifier	11 months
Minimum length of time on modifier	6 weeks
Average weekly gain per infant	5.62 oz
Number of digestive disturbances	4 (8%)

Of the four digestive disturbances mentioned two were in the form of anorexia and two of diarrhea. The cases of anorexia occurred when the infants were on 11 and 12 tablespoonfuls of the modifier, respectively, the condition was corrected by simple reduction of the amount of modifier. The two cases of diarrhea were fermentative in type, there being from 5 to 7 yellow to green semisolid to watery stools a day, one infant had excoriated buttocks. Both cases occurred when the babies were receiving 11 tablespoonfuls of the modifier. By elimination of the modifier from the formula the stools became normal in from three to five days.

A group of 100 cases was used as a control. These infants were fed a mixture of fresh cow's milk, water, and a maltose dextrin carbohydrate. The results in this group are shown in Table V.

TABLE V

Number of control cases	100
Youngest baby to which mixture was given	2 weeks
Average age at which mixture was started	2 months
Minimum length of time on feeding	6 weeks
Average length of time on carbohydrate	21 weeks
Maximum length of time on carbohydrate	9 months
Average weekly gain per case	5.8 ounces
Number of digestive disturbances	7 (7%)

Of the seven digestive disorders one was in the form of anorexia and six of diarrhea, two of which had an associated anorexia.

The anorexia occurred on a formula containing $1\frac{1}{2}$ ounces of carbohydrate and was corrected by simple reduction of this element. All of the cases of diarrhea occurred on a formula containing $1\frac{1}{2}$ ounces of the carbohydrate and were fermentative in type, consisting of from 5 to 7 green to yellow semisolid to watery stools a day. On the removal of the carbohydrate and giving a formula of one half milk and two-thirds water the diarrhea cleared in from three to four days.

COMMENT

In analyzing the results of the first group one finds of significance the average weekly gain of 5.21 ounces and percentage of gastrointestinal upsets of 6.9 per cent. In the second group we find a weekly gain of 5.62 ounces and an incidence of gastrointestinal upsets of 8 per cent.

The obvious conclusion is that Group II did better than Group I in weight gain, however, the incidence of intestinal upsets was about the same. This shows as previously mentioned the superiority of feeding this modifier as designated in the formulas of Table III, rather than using the modifier as a carbohydrate would be used. The difference in results in the two groups is due apparently to the fact that the modifier changes both the fat and carbohydrate element of the formula and a greater percentage of processed fat is available which is apparently more digestible. The method of modifying in the second group more nearly approaches the percentage contents of human milk.

In the third or control group of babies fed with a carbohydrate modifier the average weekly gain was 5.8 ounces and the incidence of digestive upsets 7 per cent. These results compare favorably with the results in Group II.

In general, it may be said that the results in feeding infants by the method of modification herein described compare favorably in weight gain with a control group of cases fed commonly used mixtures of milk, water, and carbohydrate. By using this modifier it becomes possible to add to the desired minimum of fresh cow's milk, the needed additional calories, partly as fat and partly as carbohydrate. The final mixture approaches more nearly to the proportion of food ingredients found in human milk. In addition the modifier has been reinforced in iron content so that the eventual formula contains approximately three times as much iron as is found ordinarily in milk formulas. Vitamins A and B are also found in greater quantities than in the commonly used milk mixtures.

With the use of sufficient antiscorbutic agents no manifestations of scurvy occurred.

The ordinarily used antirachitic agents were employed, and there was no greater incidence of rickets in these series of cases than in similar groups of cases reported.

TABLE IV

Number of babies on modifier	50
Youngest infant put on modifier	1 35 months
Average length of time on modifier	18 weeks
Maximum length of time on modifier	11 months
Minimum length of time on modifier	6 weeks
Average weekly gain per infant	5 62 oz
Number of digestive disturbances	4 (8%)

Of the four digestive disturbances mentioned two were in the form of anorexia and two of diarrhea. The cases of anorexia occurred when the infants were on 11 and 12 tablespoonfuls of the modifier, respectively, the condition was corrected by simple reduction of the amount of modifier. The two cases of diarrhea were fermentative in type, there being from 5 to 7 yellow to green semisolid to watery stools a day, one infant had excoriated buttocks. Both cases occurred when the babies were receiving 11 tablespoonfuls of the modifier. By elimination of the modifier from the formula the stools became normal in from three to five days.

A group of 100 cases was used as a control. These infants were fed a mixture of fresh cow's milk, water, and a maltose dextrin carbohydrate. The results in this group are shown in Table V.

TABLE V

Number of control cases	100
Youngest baby to which mixture was given	2 weeks
Average age at which mixture was started	2 months
Minimum length of time on feeding	6 weeks
Average length of time on carbohydrate	21 weeks
Maximum length of time on carbohydrate	9 months
Average weekly gain per case	5 8 ounces
Number of digestive disturbances	7 (7%)

Of the seven digestive disorders one was in the form of anorexia and six of diarrhea, two of which had an associated anorexia.

The anorexia occurred on a formula containing $1\frac{1}{2}$ ounces of carbohydrate and was corrected by simple reduction of this element. All of the cases of diarrhea occurred on a formula containing $1\frac{1}{2}$ ounces of the carbohydrate and were fermentative in type, consisting of from 5 to 7 green to yellow semisolid to watery stools a day. On the removal of the carbohydrate and giving a formula of one-half milk and two thirds water the diarrhea cleared in from three to four days.

COMMENT

In analyzing the results of the first group one finds of significance the average weekly gain of 5 21 ounces and percentage of gastrointestinal upsets of 6 9 per cent. In the second group we find a weekly gain of 5 62 ounces and an incidence of gastrointestinal upsets of 8 per cent.

76 histories, to which series he has added 2 cases from personal observation. Hunt² has discussed in detail the clinical and pathologic features of the disorder. Both papers are supplemented with bibliographies covering the entire period since Lucas³ in 1883 first reported an instance of late rickets accompanied by albuminuria. We desire to report the following case of renal dwarfism now under observation in the Children's Division of the National Jewish Hospital at Denver.

M. K., female, born March 8, 1920 at Tucson, Arizona. Admitted to our hospital, February 12, 1933. The reason for admission was given as extreme malnutrition and exposure to tuberculosis. The father is alive and well, as are two sisters, ages seventeen and eighteen years respectively. The mother, aged thirty



Fig. 1.—X ray picture of wrists, showing normal development.

nine years, born of Jewish parentage in Russia, came to America at the age of one year. In 1901 she moved from Illinois to Arizona because of tuberculosis of the right sacroiliac joint. Five or six years ago she became a morphine addict. The mother's history further disclosed that for nine years prior to the birth of the patient she had not menstruated and that she had submitted to at least two x-ray exposures with the probable object of inducing abortion. Recent examination of the mother revealed extensive healed pulmonary tuberculosis and active tuberculosis of the sacroiliac joint.

The baby was born through cesarean section during the eighth month and weighed 8 pounds, but by the tenth day the weight had decreased to 1½ pounds. In the absence of breast milk, artificial feeding was necessary. There is a vague history of convulsive seizures at intervals during the first two years of life. Eruption of the first tooth took place before the fourth month, but a diagnosis of rickets was made shortly afterward. For the past two years the patient has given little anxiety except through her astonishing failure of physical and mental development.

in 32 cases as five years and two months, and so many develop the syndrome at puberty that it is frequently known as the rickets of adolescence. Lathrop⁴ maintains that roentgenograms may be consistently negative for rickets in well-defined cases, and others consider the skeletal changes as quite independent of that disease.

SUMMARY AND CONCLUSION

A case of renal dwarfism with some unusual aspects is presented. Whether the kidney affection is of prenatal origin or was developed after birth cannot be determined. The retardation in growth and development has been so proportionate and the congenital changes have been so inconspicuous that congenital inactivity of the gonads or other endocrine structures need not be seriously considered, particularly in the absence of neoplastic invasion.

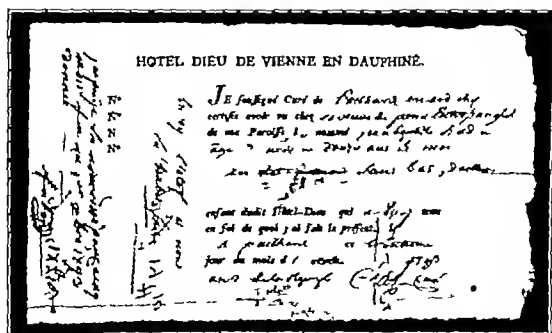
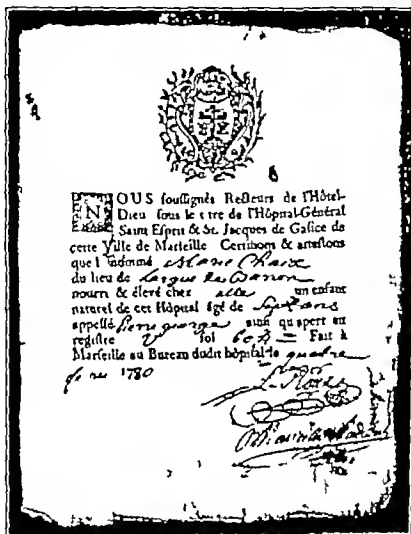
REFERENCES

- 1 Mitchell Am. J Dis Child 40 101, 1930
- 2 Hunt Am J Dis Child 34 234, 1927
- 3 Lucas Lancet 1 993, 1883
- 4 Lathrop Am J Dis Child 18 612, 1926

ANTIQUES OF PEDIATRIC INTEREST

T G H DRAKE, M.B. F.R.C.P. (C)

IN THE first certificate, dated February 4 1780, the Recteurs of the General Hospital of Saint Esprit and St Jacques of the city of Marseilles, certify that one Marie Chaux is nourishing and rearing in her home an illegitimate child, aged seven years, who was placed at



Certificates concerning nursing of illegitimate children

From the Department of Pediatrics University of Toronto, and the Hospital for Sick Children, Toronto

nurse by that hospital and in whose registers are entered particulars of the child. The second document certifies to the Hotel-Dieu of Vienne in Dauphiny that the village priest of Pailhard has visited an illegitimate child, aged about twelve years and four months, pertaining to that hospital, who was being cared for by a widow, and that the child was in good health at the time—October, 1793. Marginally, the priest asks that material and not finished clothing be sent, and the secretary of the hospital notes that he has paid the nurse for five months the sum of 17½ livres, an amount equivalent in present-day purchasing power to about 70 French francs.

Through experience the French hospitals had found that it was cheaper to place infants with nurses in their own homes than to attempt to rear them in the hospitals.

The payment for nursing varied with the age of the child. The first year, while the infant was being wet nursed, was the dearest, the nurse's fee usually remained at a somewhat lower rate from the second to the seventh year, and from the eighth to the twelfth year the fee depended on the amount of work the child was able to perform. In addition to money payments, some hospitals clothed the child until the end of its fourth year, and others until the end of the seventh year.

Schedules of wet nursing fees at various times, taken from various sources, are as follows:

In 1717, a Bourgeois of Viers records in his diary the payment of 3 livres (francs) per month for the wet nursing of his daughter in the nurse's home.

In her diary, the daughter of a Conseiller of the parliament of Paris writes that in 1747 she paid 9 livres, in 1754, 8 livres, and in 1760, 6 livres per month for the wet nursing of three successive children in the nurse's own home.

In 1802, in reply to a letter of enquiry from the mayor of Angers, the mayor of a neighboring town states that their schedule of fees for wet nursing is 5½ francs per month from birth to the age of two years, and from that time on 4¾ francs per month.

In 1823, the city of Paris paid the wet nurses 7 francs per month for the first year of the child's life, 6 francs during the second year, 5 francs from the third to the sixth year, and 4 francs from that time until the twelfth year.

In 1834 in France, the total cost of rearing a child in the care of a wet nurse from birth to its twelfth year varied in different districts from 800 to 1,300 francs.

A bill from the "Grand Bureau de Nourrices sur Lieux, fondé en 1825 par Mme Quost," dated Paris, 1880, itemizes a wet nursing account thus:

For the nurse's first month 40 francs

For the expenses of transporting the infant 30 francs

The bureau's fee 7 francs

Critical Review

DISORDERS OF INTERNAL GLAND SECRETION IN CHILDREN

Fritz B. Talbot M.D. Boston, Mass.

THE review last year presented in as simple form as possible the reviewer's interpretation of the pertinent facts then known. Since then, several significant articles have appeared and out of the enveloping fog some very definite landmarks and lighthouses have materialized to help the searcher for truth to steer his course.

Although many records of basal metabolic tests appear in the literature it is unfortunate that their value is greatly reduced and perhaps entirely cancelled because the records give only the heat production in terms of 'per square meter of body surface' and fail to give the *total heat production*. To make matters worse the metabolism per unit of body surface is recorded in deviation per cent without stating what formula is used to obtain the surface area of the body or what standards the metabolism of the subject varies from. The reviewer makes a plea that all records of basal metabolism always should record the total heat production. A brief review of the present practice in interpreting the metabolism of childhood appeared in the July 1933, Czerny Festschrift issue of this Journal.

It has not been possible to discuss the basal metabolism data in the reported endocrine cases because it is only recorded in plus or minus per cent. The reviewer had the privilege of seeing the original data of some of the important cases reported and found that the data as presented led to quite a different picture of the progress of the disease when the metabolism was charted in terms of total heat production and compared with the expected heat production for the height and for the weight.

THE INTERRELATION OF GLANDS

One is impressed on reading the endocrine literature by the number of papers which still publish beneficial results from the use of this or that gland extract in 'polyglandular syndromes'. Since accurate diagnosis of such conditions is not yet possible in most cases such reports should be considered with healthy but reasonable skepticism. Aub says in his Presidential Address before the Association for the Study of Internal Secretions in 1932 "In recent years at many clinical meetings the nihilistic point of view in regard to treatment has been actively championed. This point of view did much good by eliminating that which was false and unproved and an intelligent skepticism is always most valuable but the reaction has gone too far."

Evidence has accumulated which shows the intimate interrelation of the endocrine glands. Cushing says, "Out of all the present welter of discovery relating to the internal accretions it becomes increasingly evident that the pituitary gland holds a dominating position in the endocrine series and exercises direct or indirect control over an

unsuspected number of biochemical processes of utmost importance to the economy of the body and should one venture to single out, from many, those particular steps that in recent years did most to accelerate our progress, they were the discovery in the anterior lobe of the two inseparable hormones of growth and sex.¹⁰ These will be referred to again in the section discussing the pituitary gland.

Thyroid Gland—Since endemic goiter is attributable to a diminished or deficient supply of iodine, it has come to be considered as a deficiency disease—a deficiency of iodine. It has been recently shown that the hyperplasia which represents a stage of iodine deficiency can be brought about in animals, at least by diets rich in either calcium chloride or sodium chloride.¹⁰ The practical inference is that where iodine is lacking and cannot be replaced thyroid hypertrophy would be increased by the liberal use of chlorides in the diet. Salt should therefore be used sparingly by persons with iodine deficiency.

Hypothyroidism—Recently attention has again been drawn to the work of Mason, Hunt and Hurstthal¹³ who found mainly on adult subjects with hypothyroidism and a low basal metabolic rate, that when the blood cholesterol was higher than 200 milligrams per cent they were benefited by thyroid medication. Bionstein¹⁴ studied twenty-five normal children and found the average cholesterol values 190 milligrams per cent. He found an increased cholesterol of 277 to 782 milligrams per cent in twelve children with hypothyroidism. These values were lowered by thyroid therapy. On the other hand the literature cites numerous cases with hyperthyroidism in which a low cholesterol was not present despite a very high basal metabolic rate. Since abnormal cholesterol figures are reported in other conditions independent of the rate of heat production these findings should be held under advisement until further data are available. The reviewer depends on the clinical findings plus the rate of metabolism in the diagnosis and treatment of hypothyroidism of children.

Hypothyroidism without myxedema is commencing to attract attention in the literature. Youmans and Rivan¹⁵ have described in adults a group of symptoms which they think should suggest this condition, viz. constipation, nervousness, poor emotional control, lack of energy, vague pains localized in various regions. These patients also have a low metabolism. If the symptoms and metabolism respond to thyroid therapy the patient falls in the group of hypothyroidism without myxedema. If not the low metabolism is due to some other physiologic process. The reviewer has reported briefly a similar group found in girls, principally between the ages of fifteen and seventeen years with more obscure symptoms but with definitely low metabolism according to our present standards, who were markedly benefited by the use of thyroid. They are still being studied to determine exactly where they belong in the scheme of disorders of metabolism.

Pituitary Gland—According to many authorities the pituitary gland holds a "dominating position" in the endocrine series. It is known to contain separate hormones of growth and sex and the recent work of Evans¹⁶ also reports an adrenaltrophic hormone and a hormone which influences the sugar metabolism—a lactogenic hormone, and a thyrotrophic hormone. The significance of these new hormones to human life will not be clear until more is known about them. Cushing¹⁷ draws attention to gross and microscopic changes which result from "withdrawal or increase of the two principal hypophyseal hormones sepa-

rately." Prompt shrinkage takes place in the gonads, the adrenal cortex and thyroid after hypophyseal extirpation in the dog and rat, while hyperplasia follows injection of the growth hormones. Since the clinical effects of chromophobe adenoma are comparable to the former laboratory experiment one finds atrophy of the same glands in this condition and in acromegaly (hyperpituitarism) there is a corresponding hyperplasia.

Although an active growth hormone has been prepared, it is not yet available for clinical practice nor is it certain that it will give universally good results comparable to those seen in animals. "None of the commercial preparations which are supposed to be active 'contain more than traces of growth promoting substances even when extracted and injected into suitable animals.'" Harvey Cushing's classical article⁶ on dyspituitarism and Tracy Putnam's presentation of the present status of diseases of the hypophysis¹² both should be read in the original. They are quoted freely in this review.

The human hypophysis (pituitary) consists of two lobes, the anterior and posterior. Cushing prefers to call the anterior lobe the adenohypophysis and the posterior lobe the neurohypophysis according to the terminology of Berthelinger. This terminology will be followed here.

The neurohypophysis is the site of the formation of pituitrin. Damage of this part of the pituitary does not cause diabetes insipidus. This symptom comes from injury to the hypothalamus and with it may be associated obesity, gonadal atrophy and somnolence. It is difficult to understand why this is so, since the polyuria characteristic of diabetes insipidus is promptly relieved by the injection of pituitrin.

The symptoms of obesity, gonadal atrophy, and less frequently somnolence which are frequently called Frohlich's syndrome can be produced by injury to the hypothalamus yet the sex hormone is known to be in the adenohypophysis. This is another inconsistency which needs explanation. Attwell² after a critical study of the literature concluded that Frohlich's syndrome is not a disease of the pituitary. On the other hand, removal of the anterior part of the pituitary—the adenohypophysis—results in genital atrophy or infantilism. Tumors do not arise in the neurohypophysis.

All the diseases of the adenohypophysis are so far as is now known, due to one of three kinds of tumors—*chromophobe adenoma*, *acidophilic adenoma*, and *basophilic adenoma*. The chromophobe adenoma secretes no hormone and the symptoms of hypopituitarism resulting from it are due solely to destruction of the normal glandular elements by pressure. The acidophilic adenoma is responsible for the growth hormone oversecretion of which causes gigantism and acromegaly. The basophilic adenoma is rare and may secrete the sex principle. These adenomas may be associated with abdominal obesity, impotence or amenorrhea, glycosuria, hypertension and fractures in their later stages. Hirsutism may or may not be present.

Chromophobe Adenoma—The symptoms due solely to new growth and pressure are characteristic of chromophobe adenomas but do not appear until the later stages of acidophilic or basophilic adenomas. These tumors differ, therefore, in that the former has no symptoms at first, while the latter have initial symptoms due to excessive secretion

of their individual hormones. In the later stages when pressure and destruction take place, the symptoms of all three are affected accordingly. With increasing extension of pressure, the optic chiasm which lies above the hypophysis becomes involved, causing limited fields of vision and eventually blindness. Further afield, the hypothalamus when involved causes the train of symptoms connected with it. If sight becomes impaired, operation is necessary to preserve vision. Cushing has found on removal of the soft expanding chromophobe adenoma that the relief of pressure on the surviving normal gland substance has in some cases allowed the resumption of normal function.

Acidophilic Adenoma causes gigantism so long as the epiphyses are open and acromegaly results after they are closed. The giant reported by Behrens and Barr⁴ is a boy who at thirteen and one-half years attained a height of seven feet four inches (221.5 cm). If this type of adenoma progresses to a size which compresses the normal gland substance, sex and other functions will be interfered with. X-ray has been used with presumable success on this type of tumor by Cushing. This treatment has not yet been used in a large enough number of cases to evaluate its importance. At this writing, it gives hope of a rational method of procedure in a disease which previously had no treatment.

Basophilic Adenoma—Although the sex hormone may originate in the basophilic cells, there is evidence that it might come from elsewhere. This question will have to be settled before a clear picture of all the activities of the hypophysis can be obtained. Cushing's⁵ description of the basophilic adenoma, however, has made a picture which the clinician can readily recognize. Since very few cases are recorded in the literature, it is not possible to say if this is a disease characteristic of childhood. The youngest recorded case was fifteen years old. The disease is characterized by adiposity which spares the extremities, hypertension, impotence or amenorrhea, and fractures. Hypertension is also found in hyperplasia of the adrenal cortex and other conditions. It may be contrasted with the lowered blood pressure found in hypopituitarism of chromophobe adenoma.

The obesity of hypopituitarism does not yield to any known extract of the hypophysis.² Kenvon reports successful treatment of these types of obese cases by regulation of the diet.¹²

The Lawrence Moon-Biedl Syndrome was reviewed by Reilly and Lissner.¹⁶ It is characterized by dystrophia adiposogenitalis, atypical retinitis pigmentosa, mental deficiency, familial occurrence and skeletal abnormalities, most frequently polydactylism and syndactylism. The writers emphasize that this disease "necessitates family occurrence." They thought two of their patients improved with endocrine therapy.

Parathyroid Glands—The parathyroids supply a hormone which regulates the supply of calcium in the circulating blood and influences the phosphorus level. Complete destruction of the gland results in tetany and death unless the calcium level is maintained either by the administration of calcium or a potent extract of the parathyroid gland (parathormone of Collip).

From the clinical point of view, acute tetany is rapidly relieved by calcium chloride, but when it is due to hypoparathyroidism the cause

of this symptom is not reached without the use of parathormone. This hormone should be used with care as its dosage has not been completely established for all ages of childhood.

Hyperparathyroidism (Von Recklinghausen's Disease Osteitis Fibrosa Cystica Generalisata)—This condition has been critically reviewed from the pathologic point of view by Jaffe.¹¹ The article deserves careful reading by anyone interested.

The symptoms consist of pain, bone tenderness, deformity, tumor and spontaneous fractures of the bones. Polyuria and polydipsia are present in most cases. Associated with the increased urinary output are hypercalcemia and hyperphosphaturia. This results in decreased muscle tone, constipation and depressed feelings. Sometimes a parathyroid tumor can be detected by the physician but it is surprising how often this observation is lacking in the recorded cases. This is probably due to the small size of some of the tumors. The disease is usually first suspected by the x-ray findings and the diagnosis is made from the chemical examination of the blood.

Albright¹ has summed up the results obtained on ten cases from whom parathyroid tumors had been removed and seventy three cases from the literature. He finds that the amount of circulating calcium and phosphorus is extraordinarily constant. In the adult the calcium range is 9.5 to 11.5 milligrams and the phosphorus 3.8 to 4.5 milligrams. This constancy is made possible by drawing on the calcium and phosphorus reserve in the skeleton when these salts are lowered in the circulating blood and redepositing any excess when the salt content becomes too high. The skeleton acts in this way as a reserve station which keeps the circulating calcium and phosphorus constant. The serum calcium may be as high as 13 milligrams and the phosphorus as low as 3 milligrams in a characteristic case.

Demineralization of the skeleton may involve practically the entire skeleton but changes are most pronounced in certain bones or bony parts. The long tubular bones show the greatest degree of change and these are closely followed in frequency by the spine, sacrum, pelvis, skull, jaw bones and thoracic flat bones. The teeth are not affected.

Albright found a relationship between hyperparathyroidism and kidney stones as well as secondary kidney changes simulating Bright's disease. When a positive diagnosis of hyperparathyroidism is made and confirmed by the chemical laboratory, the tumor should be sought by the surgeon until it is found. If the chemical laboratory says that it is not hyperparathyroidism that is the final word despite clinical symptoms.

Adrenal Gland—The adrenal medulla seems to be intimately connected with heat loss from the body.¹²

Adrenal Cortex—Since the isolation of the hormone cortin (Swingle, Pfiffer and Hartman) and the demonstration of its dramatic effect on Addison's disease, a large number of physiologic investigations have appeared in the literature. The adrenal cortex is essential to life. When it is destroyed there is an extreme fall in body temperature, a marked loss of weight in dogs. These symptoms can be overcome by injections of cortical extract.

Tumors of the adrenal are often malignant adenomas. The characteristic symptoms are hypertension, hypertrichosis, deviations of the

secondary sex characteristics such as masculinization of women. Tumors are sometimes associated with precocious sexual development and pseudohermaphroditism, especially in the female.

Although *adrenal insufficiency* is rarely seen in young children, the possible applications in the future to pediatric problems justify a brief discussion of it here. Hartman⁹ says that in cortical insufficiency, as *asthenia* develops insidiously and is the first symptom to appear. This weakness was shown to be due to involvement of the muscular tissue itself. The circulation soon becomes involved and in later stages the heart action may be feeble and the blood pressure low. Finally, the function of the kidney becomes weakened and fails. The energy metabolism is lowered and can be brought back to normal by the administration of cortin, it cannot be raised above normal level by this hormone. Cortin is essential for growth and when absent the resistance to toxins is diminished. It apparently has some beneficial action on Vitamin B and C. Pigmentation of the skin, as is seen in Addison's disease, seems to be due to lack of cortin and to be benefited by its administration. In adrenal insufficiency the blood sugar is frequently low. Hartman also has reported a new hormone called "cortilactin" which influences the secretion of milk in rats.

The data given above is confusing for the practicing physician but is of extreme interest to the physiologist. Today this knowledge has no practical bearing on pediatric problems, but it has opened a door which promises many possibilities for the future.

Sex Glands—Novak and Long¹⁴ made a survey of the tumors of the sex glands and found that granulosa cell tumors of the ovary have a feminizing tendency due to the production of folliculin. Arrhenoblastomas have a defeminizing tendency.

The *ovary* is activated by the sex hormone of the adenohypophysis thus stimulating the maturation of the graafian follicle. This starts the ovarian hormone called theelin by Doisy—folliculin or estrin by others. Theelin therefore, favors menstruation. Progesterin (corporin-lutin) is then formed to stimulate the growth of the endometrium during the second half of the menstrual cycle. Theelin then inhibits the sex secretion of the adenohypophysis and menstruation takes place.⁵ Theelin is apparently now available in physiologically active preparations and progesterin is not.

Prolan is found in the blood and urine of pregnant women ("Aschheim and Zondek's Test for Pregnancy").

Although it has been shown that there is a definite interrelation of the various glands in the endocrine system, it is not clear in most cases just what that relation is. Attempted therapeutics would be simplified enormously if one could answer the old and simple conundrum "which came first, the hen or the egg?" As in other fields of medicine the best results can only be obtained by correcting the cause. Little can be said for treating the symptom alone. It seems probable that as knowledge progresses to the point where the secondary effects of primary glandular overaction or underaction are completely understood that the term "polyglandular syndrome," as it is used today, will disappear from the literature and be forgotten as are the quackeries of the past.

REFERENCES

- 1 Albright, Fuller Hyperparathyroidism Its Diagnosis and Exclusion N. E. Jour Med 209 416 1933 Aub Bauer Ropes Ellsworth and Albright Jour Clin Invest. 7 184 1930 11 1011, 1932.
- 2 Attwell Endocrinology 16 24 1932
- 3 Aub, Joseph C Endocrinology 16 507 1932
- 4 Behrens and Barr Endocrinology 16 120, 1932
- 5 Bronstein L. P. Studies in Cretinism and Hypothyroidism in Childhood I Blood Cholesterol J. A. M. A 100 1661 May 27, 1933
- 6 Cushing, Harvey Dyspituitarism Arch. Int. Med. 51 487 1933
- 7 Evans Trans Congress Am. Phys & Surg Washington 15 25 1933
- 8 Finkel, H. S. The Present Status of Our Knowledge of the Ovarian Hormones N. E. Jour Med 209 473 1933
- 9 Hartman, F. A. Certain Functions of the Adrenal Cortex. N. E. Jour Med 209 480, 1933
- 10 Hibbard Arch. Surg 28 649 1932
- 11 Jaffe, H. L. Hyperparathyroidism (Recklinghausen's Disease of the Bone) Arch. Path. 10 63, 236 1933
- 12 Kenyon, Josephine H. The Hypopituitary Type of Obesity Treated Without Glandular Medication J. A. M. A 101 97, July 8 1933
- 13 Mason, Hunt, and Hurxthal Blood Cholesterol Values in Hyperthyroidism and Hypothyroidism. Their Significance N. E. Jour Med 203 1273 1930
- 14 Novak, E., and Long J. H. Ovarian Tumors Associated With Secondary Sex Changes Granulosa Cell Carcinoma and Arrhenoblastoma, J. A. M. A 101 1057, Sept 30, 1933
- 15 Putnam, Tracy The Present Status of Diseases of the Hypophysis N. E. Jour Med 209 486 1933
- 16 Reilly and Lissner Endocrinology 16 337 1932
- 17 Wyman and Sinden Soc. Exp Biol. & Med. 30 61 1932
- 18 Youmans and Rivas Ann Int Med 5 149, 1932

American Academy of Pediatrics

Proceedings

THIRD ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

MONDAY AFTERNOON SESSION

JUNE 12, 1933

Round Table Conference on Blood Disorders Characterized by Bleeding

Leader Dr Thomas B Cooley Assistant Dr Heyworth N Sanford

The meeting was called to order at 2 P M by the Chairman, Dr Thomas B Cooley, Detroit

DR COOLEY—We cannot cover all the disorders of the blood in any one round table discussion Last year we talked about the anemias of infancy This year we are going to take up the disorders associated with bleeding It is not our idea to try to tell you all about the subject What we want to do is to lay out a framework for discussion and have you all join in

There seems to be no very good name for this group of disorders They are sometimes spoken of as "hemorrhagic diatheses," but that is not a particularly good expression I like the German name better—'Blutungsabel' It seems to express our meaning better than any term in common use with us

Of course, not all of these diseases are, strictly speaking, disorders of the blood, but when we are considering the hemorrhagic disorders, though they have widely differing etiologies, the resemblances in symptomatology make it simpler to group them together

Any consideration of the bleeding disorders requires some conception of the blood clotting mechanism, which is so often involved in hemorrhagic states I shall try first to lay some foundation for discussion of that process

The ideas about the clotting mechanism are, as you know, still quite confused There are plenty of theories as to how clotting takes place, but the problem is not settled and some of the theories are quite contradictory Some are complicated and hard to understand The reason for the multiplicity of theories is doubtless that we have not yet sufficiently accurate methods for studying many of the questions involved Problems of colloid chemistry and physicochemistry are encountered which are still not very well understood and not susceptible of convincing demonstration by present methods

The principal differences in the theories depend on whether the clotting process is looked upon as a series of chemical reactions, or a group of physicochemical phenomena, or a combination of these two, or whether there is a ferment action or something analogous to it involved There also is not complete agreement as to observed facts, and there are some generally recognized facts not explained

by any of the theories. Some of the theories are too elaborate to attempt to go into in a meeting of this kind.

Shown on the slide is what one might call the classic theory in its simplest form. It is quite generally agreed I think that as I have shown in the chart on the slide, there are present in the blood as it circulates prothrombin, calcium and fibrinogen, and probably a small amount of the lipid cephalin and that the fluidity of this mixture is maintained by something for which we may use the term antithrombin without too great insistence as to its precise nature.

When the blood is shed, changes take place which are represented on the lower part of the slide and which probably are started by the disintegration of the platelets. We agree that they contain cephalin probably an additional amount of prothrombin, and therefore add this to the shed blood as compared with the circulating blood. The clot the fibrin formation itself is almost universally agreed to be due to a combination of thrombin and fibrinogen. Whether this is an actual chemical reaction or whether it is a physicochemical adsorption process is another matter. The classic theory in its simplest form is that when blood is shed the platelets become agglutinated and undergo disintegration with the liberation of cephalin, which in the presence of calcium (probably serving as a catalyst) converts prothrombin to thrombin. Thrombin and fibrinogen unite to form fibrin which is deposited as a network of long needles enmeshing the corpuscles. Ultimately this mass of fibrin needles and corpuscles contracts, producing the firm clot and extruding the serum.

This diagram does not show some of the more recent developments of this theory, such as the formation of an inert 'metathrombin' by a union of thrombin and antithrombin and some other anticoagulant reactions which Howell has brought out. It is the emphasis put upon the anticoagulants that chiefly distinguishes Howell's ideas of clotting from those of some other workers. His theories would make a very complicated diagram and at present they are hardly sufficiently proved to have important clinical application. It is fairly clear, however, that there must be in the blood one or more substances having an anticoagulant action and that serve to keep the blood in fluid form during its course in the circulation. How one may suppose they exert that action must depend on whether one accepts the idea of the clotting process as a train of purely chemical reactions including chemical neutralization of the anticoagulant factors by products of platelet disintegration or whether one agrees with the physicochemical explanation of the upsetting of the delicate equilibrium of a balanced colloid complex by the introduction of the new factors introduced from the platelets.

Bordet has been one of the important workers in the study of clotting and his theory deserves mention. (Slide) He makes use of a different terminology derived from the old idea of conglutination as a ferment action, though he does not subscribe to that idea. For prothrombin and cephalin he uses the terms 'serozyme' and 'cytozyme,' and thinks they unite in the presence of calcium to form thrombin. He lays especial stress on contact of the blood with a foreign surface in the wound (or in the test tube). The importance of this contact is unquestionable and is the reason for the use of paraffined tubes in the laboratory to minimize clotting. He postulates a 'proserozyme' which in our terminology would be pro-prothrombin," which in contact with a foreign surface in the presence of calcium becomes serozyme then serozyme and cytozyme form thrombin which unites with fibrinogen to form fibrin.

Mills, of the University of Cincinnati has busied himself with the clotting problems for a long time, and has taken up and developed the ideas of the Engelman-Woodbridge. He is a careful worker, and I think deserves attention, though his theories seem not to have gained much acceptance.

(Slide) He believes that two independent clotting processes go on at the same time. The clotting is inaugurated by a direct combination of what he calls tissue fibrinogen with the blood fibrinogen. Tissue fibrinogen is supposed to be a combination of cephalin with varying proportions of protein, and to be derived both from platelets and from tissue juices. The union of tissue fibrinogen and blood fibrinogen he believes can happen directly without any of the preliminary reactions of the classic theory, and the production of small amounts of fibrin in that way sets off the classic mechanism.

The classic theory as I presented it in the first slide seems to be the one commonly accepted in this country, and is as good as any for the interpretation of clinical phenomena.

I suppose most of you have seen articles by Kugelmass regarding his idea of measuring increased or decreased coagulability of the blood by means of a "clotting index." He seems to have been a pupil of Bordet's, and has done a good deal of work in New York on this question of measuring coagulability, both as a diagnostic procedure and as a preoperative precaution. He derives what he calls a clotting index by taking the product of the factors which favor clot formation and dividing by the anticoagulant factor, antithrombin. (Slide) The normal prothrombin index is given an arbitrary value of one. The fibrinogen index is five tenths, because that is not an arbitrary value. It represents the ratio of the refractive power of the serum to that of the plasma, which is normally one half. The prothrombin index is the relation of the prothrombin time in a particular blood to that of a normal control. All theories agree in assigning to the platelets the most important place in initiating the clotting process. Kugelmass measures the platelet value by taking 200,000 as the normal count, and 50 per cent as normal disintegration in one hour, thus getting a normal figure of 100,000 for active platelets, to which he assigns a value of one in his index. The antithrombin, again, is given a normal index of one. I shall not go into the methods of determining these values, which are to be found in laboratory manuals. The values assigned give a normal index of five tenths, from which Kugelmass allows a variation of two tenths as within normal range.

This scheme is, I think, rather a good one—not so important in the diagnosis of the marked disorders as in minor things, such as the tendency to oozing after a tonsil operation, tooth extraction, or something of that kind. Here is a sample of how it works out. (Slide) This was a hemophilic patient. The prothrombin index was 0.44, fibrinogen, 0.5, platelet lysis 10 per cent (index 0.2), antithrombin index 1.2. The clotting index is 0.036. The clotting time of the patient's blood was thirty minutes. Kugelmass emphasizes the very great lowering of the clotting index in hemophilia as compared with almost any other condition. It is evident, however, that in thrombocytopenic purpura with a very low platelet count the index will be fully as low.

With this rather sketchy background of the clotting mechanism, I wish to say some things about hemophilia. Dr. Sanford is to talk of some of the other disorders.

You all know that hemophilia is the great example of hereditary disease. It is also an example of sex-linked heredity, never transmitted direct by the male, but through the daughters of the male to their male offspring. Or, it may go through two or more female generations and finally appear in male descendants.

(Slide) Here is a rather simple family tree of a hemophilic family, in which you may see how these things go. For instance, you will see in one of the lines of female descent how the trait has gone through two female generations to become manifest finally in their male descendants. This does not show some of the things that Dr. Birch speaks of, and that I have not seen mentioned elsewhere.

I should be interested to study enough hemophilic trees to see how well her statements are justified. She says the study of hemophilic trees seems to show that hemophilic males tend to have more female children, and their daughters to have more males, and that the chances are that about two out of three of these male descendants will be hemophilic. That seems to me, on theoretic grounds, rather doubtful, and I should like to see it demonstrated.

The question is always coming up whether there is any possibility, according to the laws of heredity, of hemophilia ever being transmitted by the hemophilic male to his own sons, or whether on the other hand, there is any possibility of a female hemophilic. Apparently, so far as our present ideas of hereditary transmission are concerned, there is no possibility of the male transmitting hemophilia directly. There seems to be a remote possibility of the female hemophilic. That it has not been definitely proved to occur has been ascribed to the fact that it would involve a union of two hemophilic strains, and that the bleeding tendency in that case would be so marked that the child probably would not be born alive. This may be a plausible explanation.

Though hemophilia is not a common disease its clinical features are quite familiar. The tendency to prolonged bleeding from slight trauma is the most striking feature, and it may be observed very early in life. There are on record plenty of cases of fatal bleeding from circumcision in hemophilic families, enough so that it has been necessary to make regulations to prevent it. The tendency to bleeding from minor trauma is not usually observed in early infancy, probably because infants are not often subjected to trauma, but it does appear fairly early in life. While it is the most common symptom of hemophilia, it is not the only characteristic type of bleeding. Bleeding into a muscle without definite trauma beyond some slight muscle strain is, for instance, not an uncommon feature. Perhaps the most striking thing in long time observation of hemophiles in the clinic is that nearly all of them in time have joint hemorrhages. First one sees them with the ordinary bleeding from trauma, and presently one finds them developing hemarthrosis in one or another joint, and this is a progressive thing, with repeated hemorrhage and increasing deformity of the joint so that in any hemophilic family one is fairly sure to find several cripples of this type.

One of the most troublesome features of the clinical picture is the tendency to bleeding from the gums. Whether the bad teeth which nearly all hemophilic children have are to be ascribed to malnutrition from lack of proper exercise I do not know, but certainly their teeth are bad and they tend to produce hemorrhage by wounding the gums. One of the difficulties in the handling of hemophilia is the bad teeth, the obvious need for their removal, and the danger of severe bleeding from the ordinary dental operations. This is perhaps the most troublesome thing in the handling of the hemophilic child in the clinic. We have at present no satisfactory method of meeting this problem, and it is a question whether to let the teeth go and have the gums subject to bleeding from trauma or to have the teeth removed and take the chance of dangerous hemorrhage.

I need not tell you that these hemorrhages are not only serious, but quite often fatal. It is not so very uncommon to read in the paper of a child bleeding to death from hemophilic hemorrhage, or being ill for a long period. Just the other day I noticed that one of the children in the family of the King of Spain, (as you know that is one of the hemophilic families) had been for ten days or two weeks in the hospital with bleeding which was still making trouble. The hemorrhage does not ordinarily tend to stop spontaneously until the process of repair of the wound is complete. They are not stopped by clotting. When an apparently firm clot has formed the oozing continues around its edges. Apparently, it is something like trying to make glue adhere to a wet surface.

(Slide) He believes that two independent clotting processes go on at the same time. The clotting is inaugurated by a direct combination of what he calls tissue fibrinogen with the blood fibrinogen. Tissue fibrinogen is supposed to be a combination of cephalin with varying proportions of proteau, and to be derived both from platelets and from tissue juices. The union of tissue fibrinogen and blood fibrinogen he believes can happen directly without any of the preliminary reactions of the classic theory, and the production of small amounts of fibrin in that way sets off the classic mechanism.

The classic theory as I presented it in the first slide seems to be the one commonly accepted in this country, and is as good as any for the interpretation of clinical phenomena.

I suppose most of you have seen articles by Kugelmass regarding his idea of measuring increased or decreased coagulability of the blood by means of a "clotting index." He seems to have been a pupil of Bordet's, and has done a good deal of work in New York on this question of measuring coagulability, both as a diagnostic procedure and as a preoperative precaution. He derives what he calls a clotting index by taking the product of the factors which favor clot formation and dividing by the anticoagulant factor, antithrombin. (Slide) The normal prothrombin index is given an arbitrary value of one. The fibrinogen index is five tenths, because that is not an arbitrary value. It represents the ratio of the refractive power of the serum to that of the plasma, which is normally one half. The prothrombin index is the relation of the prothrombin time in a particular blood to that of a normal control. All theories agree in assigning to the platelets the most important place in initiating the clotting process. Kugelmass measures the platelet value by taking 200,000 as the normal count, and 50 per cent as normal disintegration in one hour, thus getting a normal figure of 100,000 for active platelets, to which he assigns a value of one in his index. The antithrombin, again, is given a normal index of one. I shall not go into the methods of determining these values, which are to be found in laboratory manuals. The values assigned give a normal index of five tenths, from which Kugelmass allows a variation of two tenths as within normal range.

This scheme is, I think, rather a good one—not so important in the diagnosis of the marked disorders as in minor things, such as the tendency to oozing after a tonsil operation, tooth extraction, or something of that kind. Here is a sample of how it works out. (Slide) This was a hemophilic patient. The prothrombin index was 0.44, fibrinogen, 0.5, platelet lysis 10 per cent (index 0.2), antithrombin index 1.2. The clotting index is 0.036. The clotting time of the patient's blood was thirty minutes. Kugelmass emphasizes the very great lowering of the clotting index in hemophilia as compared with almost any other condition. It is evident, however, that in thrombocytopenic purpura with a very low platelet count the index will be fully as low.

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ourselves of any real effect. It is an easy treatment to carry out, and deserves consideration as one of the possibilities for the routine handling of the hemophilic, as this is a condition in which one wishes to do everything possible.

Another treatment which has been in the limelight lately is that of the use of ovarian extract. This is not new. It was based originally on the peculiar sex limited heredity of the disease, and the not unnatural assumption that the sex hormone might have something to do with the immunity of the female. The new thing is the observation by Dr. Carrol Birch that the small amount of the female hormone said to be present normally in the male urine is absent from the urine of the hemophilic. Sho and some others have reported remarkable results from intramuscular injection of the hormone as a therapeutic agent, and I suspect that everyone who has hemophiliacs in his care has given it a trial or considered doing so.

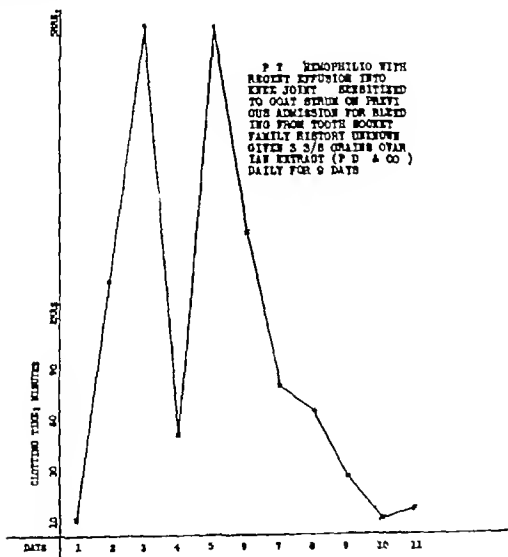


Chart I

We have been trying it on some of our hemophiliacs recently. I do not think that our results are at all conclusive because we have not enough of them, but I should like to show you what we have done.

Chart I shows the curve of daily determinations of clotting time in one of our patients who came in just after an effusion into one of the knee joints. Bleeding had stopped when he came in and we kept him to make sure that it was not going to recur utilizing the hospital stay to observe the effect of daily injections of ovarian extract on the clotting time. The dose here was one ampule containing three and three-fifths grains of a preparation of the whole ovary made by Parke Davis & Co. The chart shows very nicely the wide fluctuations in the clotting

of a difficulty which we have encountered in other hemophiliacs, and for which I have no definite explanation. We use venous blood for these determinations. At times there is such a marked tendency to thrombosis at the point of puncture that we cannot use the vein. I think that this may be a mechanical effect of platelet agglutination at this point without disintegration.

I have not charted one case, treated before we began to try the ovarian extract. This was another in which we wished to extract teeth and it was our first trial of the protein sensitization method. We sensitized the patient drew two teeth and produced a sharp reaction with intradermal serum. The child bled very badly, and needed three large transfusions to save him.

Our results with these newer treatments do not seem to have brought out much in their favor. I do not feel, however that we have gone far enough with them to draw definite conclusions and I am inclined to try them further. It may be that we have not used large enough doses of ovarian extract. I believe that Birch has given as much as eighty grains gauging her dosage by the clotting time. After our experiences with the wide variations in this measurement I do not see how the dose can be satisfactorily gauged by it. We got no effect at all from single doses and daily doses of eighty grains would be a pretty expensive method.

The present status of the therapy of hemophilia would seem to be that we have two methods for which there is enough favorable testimony so that they deserve further careful trial. We cannot, however depend on them to prevent or to check severe bleeding and are not safe in undertaking any surgical procedure on a hemophilic without being prepared to apply the only measure which has been proved to be reliable—transfusion. I think that we have sometimes made the mistake in transfusing for hemophilic hemorrhage of giving too small transfusions or of not giving them early enough. In both hemophilia and purpura I believe that large transfusions are better than small ones and I am sure that they are more effective if they are given early, without waiting to see how bad the bleeding is going to be.

We will pause here for discussion before listening to Dr. Sanford.

DR. H. B. HAMILTON (OMAHA, NEBRASKA)—My understanding is that Dr. Mills injects the serum near the bleeding point, is that correct?

DR. COOLEY—Yes but it depends upon where the bleeding point is and can not always be done. It is possible only in the minor superficial injuries such as bleeding from scratches, etc. As a matter of fact, we have had very little occasion to treat those things.

Another thing about hemophilia is that very commonly we have bleeding from some one of the mucous membranes—the frenum of the tongue, the gums or some similar place where intradermal injections are not practicable. The same difficulty is met with in nosebleeds.

DR. MARTIN D. OTT (DAVENPORT, IOWA)—Can you make local applications for nosebleeds?

DR. COOLEY—I do not believe it would be possible. A thing we have tried with bleeding gums is to pack them with tissue fibrogen. We have never had any effect from it. One would think that putting a substance which really contains a good deal of cephalin right into the bleeding cavity might help but we have never been able to see that it did. We have had no luck with tissue fibrogen given either by mouth, by local injection or direct local application.

DR. STERLING H. ASHMUN (DAYTON, OHIO)—I have been very much interested in this work of the Cincinnati group, having heard them discuss their

claims A discussion came up in a meeting, as to the best method of sensitizing a child For instance, a young baby might be sensitized to tuberculin Since most people are sensitized to tuberculin early in life, it might be a good thing to use intradermally as the substance to which the child might be sensitive That might be tried early in life They also found the use of ovarian extract to be a help We should have thought of this a long time ago since the female does not have hemophilia and the ovarian substance is the one thing she probably has that the male does not. Certain workers believe that females sometimes do have what they consider to be hemophilia.

If there has been more than one ancestor with hemophilia, the female offspring are all the more liable to have hemophilia We should advise that hemophiles should not marry At the Central States Pediatric Society meeting last year, the use of muscle tissue from the individual to stop the hemorrhage was reported That would be a good source for tissue fibrogen in any individual when an operation was contemplated If a piece of the tissue could be planted or fastened right into the wound it might help, even placing it in a tooth socket might help to control the hemorrhage Since ovarian extract is involved, might not those cases in which the female shows a tendency to hemophilia or purpura show some involvement of the pituitary? Dr Cooley mentioned the finding of poor teeth so constantly in hemophiles. That suggests also a deficiency in calcium metabolism as well as a capillary penetrability We have had favorable results in preventing, or in lessening the frequency of ordinary hemorrhage in circumcision by the use of a high protein diet in the first few days of life I am thoroughly convinced that the high protein diet does aid even in hemophiles, in lessening the danger of hemorrhage In one case in which the capillary clotting time was four minutes, we found after circumcision no clotting whatever, until after the injection of fibrogen, then in five minutes there was good clotting and the patient made a good recovery

DR T COOK SMITH (LOUISVILLE, KY) —Of what does the proof of diagnosis in the very young consist?

DR COOLEY —I think in the very young infant the diagnosis is bound to be a little doubtful On the whole, two things are probably more important than any of the others First, the great prolongation of venous clotting time This however, has to be measured more than once, because you might run into one of these periods where the clotting time is pretty short, like some of those I showed on the charts Therefore, you would have to make more than one test to insure accuracy, although if the child is actually bleeding, the chances are that you will find the clotting time prolonged Second, failure of platelet disintegration is equally important in the hematologic diagnosis and the prolonged anti-thrombin time, which apparently goes with the delay in platelet disintegration While it is a somewhat difficult thing to measure, I really think failure of platelet disintegration is perhaps the best test we have of definite hemophilia A very low clotting index is very strongly suggestive

DR SMITH —Is there any experience in your clinic to show that there are female hemophiles?

DR COOLEY —We have no experience indicating that there are There are some reported observations of disturbances in the clotting mechanism in females of hemophilic families but I am not aware of any evidence of true hemophilia Dr Gorter, what do you do with hemophilia in your clinic?

DR E GORTER (LEIDEV, HOLLAND) —We have had almost the same experience you have had in regard to hemophilia We have also tried ovarian extract in the

hope it would be useful but we could not find any definite results. I have been asked, and I would like to ask you whether a different form of preparation of the ovarian extract might account for difference in results? I feel as you do that it is very important to make large transfusions and to do so early. If you apply transfusion from the very beginning of bleeding I think results are temporary. I think they last almost one week and then it is necessary to repeat it.

May I ask another question with regard to the disintegration of platelets? You will find in the literature a description of thrombasthenia by Glanzmann, which indicates that failure of platelet disintegration may occur in other conditions than hemophilia. Do you believe in the existence of this thrombasthenia as a cause of purpuric conditions? Would this somewhat complicate the value of the prothrombin test or the disintegration of platelets in the diagnosis of hemophilia?

DR. COOLEY —I have no knowledge of that disease except from Glanzmann's description, so I am afraid I could not answer. I think it must be very rare. As to transfusion, I would not have you think I am not optimistic about transfusion. I think it is the best treatment we have. We use it freely and we have never lost a patient from hemophilia.

As to the preparations of ovarian extract, Dr. Birch has used a good many of these. As you noticed, we used three different ones. I do not remember that she has had definitely more favorable results from one than from another. She simply stated, as I remember, that she tried a number of preparations and she tried also some very large doses and seemed to think the doses should vary in accordance with the clotting time.

From the clotting times I charted, I do not see how you could use them as a basis for your doses as when you see a child with a clotting time one day of ten minutes and the next day of five hours, your choice is certainly doubtful. We apparently got as good results from the preparation of which we gave somewhat less than four grains at a dose, as we did from the other preparation of which we gave twenty six grains or from the supposedly pure Thellin.

DR. GORTER —Is there any confirmation by animal experimentation of the reported testicular atrophy after ovarian extract administration?

DR. COOLEY —I have not been able to learn of any. I have inquired of men working with ovarian extract in animals but have not heard of any definite observations on this subject.

Do any of you want to go into the question of the clotting mechanism itself?

I have a feeling that a discussion on theories of clotting does not get us very far. I mean to say that the observed facts are pretty generally recognized, and that beyond that we get into a region of theory which cannot be valuable clinically. I feel the clinician may just as well rest where he is for the time being. Now things are coming up all the time.

The relation of carbohydrate metabolism to clotting is one of the things which seem to be getting quite a bit of discussion in some of the foreign clinics and out of which I have not been able to get much so far.

DR. GORTER —Is it not possible that there is not only failure of platelet disintegration but some more general disturbance of reticuloendothelial function?

DR. COOLEY —We have by no means reached a complete understanding of the bleeding disorders. I think that all of us who have busied ourselves with the blood have come in recent years to feel that eventually we may find that several of the disorders which we do not understand very well are really dependent on dysfunction of the reticuloendothelium.

One of the things about the clotting mechanism which no theory explains satisfactorily is the failure of clot retraction with a scarcity of platelets. Mills, who looks on clotting as a reversible reaction, and believes that fibrin disintegrates with liberation of thrombin, thinks that the explanation may lie in this (I do not quite understand his reasoning). Howell says that the only suggestion he has is that it may be a matter of a quantitative lack of fibrin in the clot.

If there is no further discussion, I will ask Dr. Sanford to go on with the purpuras.

Purpuras

DR. HEYWORTH SANFORD (CHICAGO).—In the very loose classification of conditions we speak of as purpuras it seems obvious that we are dealing with a number of etiological factors, which it should not be difficult to separate. In one recent article, however, all the purpuras are thrown into one large group, without recognition of the platelets as an etiological factor, so that it is evident there is still a good deal of confusion.

It seems to me the best method of classification is to divide them into two groups: first, the thrombocytopenic type, in which the platelets are distinctly diminished, and second, the nonthrombocytopenic type, in which there is no change in the clotting factors.

In the first group, that in which the platelets are diminished, we have a primary, "idiopathic" type, in which there is no change in any of the constituents of the blood except the platelets, and various secondary forms, in which the blood shows changes due to the primary disorder. The platelets are always markedly reduced, and the bleeding time as a rule is lengthened, usually to more than seven minutes. How low must the platelet count be to cause danger of bleeding? Most writers agree that when the count falls below 100,000, purpura may develop. McLean published in 1921 a study of twenty-one cases, all of which the count was below 100,000, the lowest being 10,000.

The secondary thrombocytopenias may be subdivided again into a group in which the platelet deficiency is due to interference with marrow productivity by tumors, leucemic infiltrations, aplastic anemia, etc., and another in which infection plays the chief etiologic rôle. Certain acute infections, diphtheria, scarlet fever, influenza, and notably the streptococcus infections, are particularly prone to lower the platelets. *Streptococcus foci* which remain for any time almost invariably cause a marked reduction. Among the chronic infections, tuberculosis and syphilis are likely to have this effect. In this group, we are evidently dealing with conditions in which treatment must be directed to the underlying cause.

The most interesting member of the thrombocytopenic group is the so-called essential thrombocytopenic purpura, or Werlhof's disease, one of the first blood disorders to be studied. Werlhof published his description in 1735. The chief characteristics are purpura, possibly some fever, increased bleeding time and decrease in platelets. The important thing is the decrease in platelets, the primary cause of the condition. When clot formation in this type of purpura is studied with the ultramicroscope the fibrin threads are seen to be deposited, and clotting seems to proceed in the normal way, but the clot which is formed is peculiarly soft and does not contract with separation of the serum. Consequently, bleeding continues for a longer time.

Washed platelets from a patient with essential thrombocytopenic purpura mixed with serum from a normal person from which the platelets have been removed will cause that serum to clot, while washed platelets from a normal person will cause normal clotting of the blood of the purpuric patient. These facts

are proof that the difficulty does not lie either in any defect in the patient's platelets or in anything in the plasma but wholly in the shortage of platelets.

Deficiency of platelets must be due to one of two reasons either the production in the marrow is inadequate or they are destroyed somewhere in the circulation. In the secondary thrombocytopenias defective production is probably to blame. Against this as the cause of essential thrombocytopenia is the fact that in autopsies on patients dying from this disease we do not find evidence of disturbance or destruction of platelets in the marrow. Furthermore in secondary thrombocytopenia due to aplasia or displacement of marrow by tumors the purpura is never so severe as in the idiopathic form.

The other explanation is that of destruction somewhere in the circulation. The reticuloendothelial system, a conception for which we are indebted to Aschoff, is composed of peculiar cells found in spleen, liver, lymph nodes and other similar tissues, the spleen containing the greater proportion of them. The large mononuclear phagocytes which are known to destroy platelets are a product of this system. If trypan blue is injected into an animal these cells take it up and become "blocked." This is followed by an increase in the platelets. Cole in 1907 developed an antiplatelet serum. If this serum is injected into an animal there is an immediate decrease in platelets unless the spleen has first been removed in which case there is no decrease.

We are justified, therefore, in concluding that in essential thrombocytopenic purpura the platelet deficiency is due not to defective formation but to destruction by the reticuloendothelium in which the spleen has the chief part.

This type of purpura has a seasonal tendency. It is seen more often in the spring. Again it is somewhat more common in females, and is likely to manifest itself before the third decade of life. The fact that it is a disease characterized by spontaneous remissions probably accounts for the great variety of treatment to be found recommended in the literature.

The idea of dietary treatment is old. Willan in 1801 advised fresh air and abundant diet. Engelmann recommends a high protein regime. Almost all of the vitamins have had their advocates. Phillips in 1931 reported platelet increase following viosterol. Cramer and Drew in 1923 reported platelet increase and Booy and Moise in 1920 platelet increase and remission of symptoms following ultraviolet irradiation. This has not been confirmed by later observers. Jones and Tocantins, reporting a series of cases in 1933, mention two cases they were unable to control by transfusion in which the platelet count was increased by pituitary extract. Three interesting carefully studied cases have been reported in which cure seems to have followed the administration of *bothrops antivenom*. As the patients were soldiers serving in the Canal Zone, there may have been some unrecognized factor though the symptoms were typical of essential thrombocytopenia.

There is general agreement as to the advisability of clearing up foci of infection. Secondary purpuras are often caused by such foci and recurrences of essential thrombocytopenia are likely to be initiated by flare-ups of infection.

Transfusion is almost universally considered the method of choice for control of the immediate attack. I was interested in Dr. Cooley's remarks about the desirability of large transfusions, because Jones and Tocantins advocate frequent small ones. They say they have had just as good results from 25 to 200 c.c. of blood injected at frequent intervals as from 500 to 1,000 c.c. at longer intervals. They say also it must be given intravenously, which is not in agreement with our experience. We think we have had as good results with intraperitoneal injections as with intravenous administration.

Finally, we come to the question of surgical intervention by removal of the spleen. While this seems logical, and most writers report favorable results, the statistics are not so good as we should like them to be. I think that Whipple's figures published in 1926 are the best. He reported results of splenectomy in eighty one cases, most of which he had been able to follow for five or six years. Of the eighty one patients, 50 per cent were definitely improved after operation, and of that 50 per cent, 60 per cent were permanently benefited.

There are indications for and against splenectomy. Most observers think that if it is possible to control the condition by other means, such as transfusion, this is advisable, though it is not wise, of course, to wait too long. McLean thinks that splenectomy should be performed in two types of cases, first, in those in which the bleeding is so free that the patient will evidently soon be moribund, and second, in the chronic case with frequent relapses and resultant secondary anemia which is interfering with the patient's development.

Payr, in 1931, reported thirty four cases in which the splenic artery had been ligated. The results, though slower, were apparently very good, and the operation is less dangerous because the shock is less. There have been no reports of thrombosis of the artery. This may prove to be the treatment of choice in selected cases.

The prognosis in this type of purpura varies greatly. The patients seem to have relapses alternating with periods of comparatively good health. McLean had four deaths in his series of twenty five, and Jones and Tocantin nine in fifty three cases.

So much for the thrombocytopenic purpuras.

In the second large group we have the cases in which there is neither platelet lack nor any other derangement of the clotting mechanism. Certain of these have a definite etiology. Malnutrition, lack of vitamin C and other similar conditions may cause purpura. Some infections, particularly respiratory, not uncommonly have this effect, as do mechanical factors such as varicose veins, certain tumors and pertussis.

Most of the cases of nonthrombocytopenic purpura have no such definite etiology. By far the largest number of all the purpuras fall into this class, and they seem to represent different grades of the same condition. We are all familiar with the so called purpura simplex, of which we see a good deal, and which has no symptoms except purpuric spots—large black and blue spots on the extremities, or showers of smaller spots all over the body. There may be a little falling off of appetite, usually some nervous disturbance, but that is about all. The condition lasts from two days to two weeks and then clears up. There are almost always associated allergic symptoms such as urticaria or other manifestations of the allergic constitution. Going a little further, we have the "arthritic" type, with effusion of blood into the joints and pain apparently out of proportion to the swelling. This form, though more severe, runs the same course. Then we have the abdominal type known as "Henoch's purpura," in which, in addition to purpuric spots and joint symptoms there is abdominal pain, diarrhea and vomiting and bleeding from the gastrointestinal mucosa.

Though there is no universal agreement, these forms of purpura are quite generally believed to be allergic phenomena. It is usually said there is no change in the blood elements. This is certainly true so far as the platelets are concerned. We have recently had a case of Henoch's purpura in which, in testing the clotting factors in the way Dr. Cooley has described, we found the fibrinogen decreased to less than half normal value. Lack of fibrinogen in the blood is usually evidence of some disturbance of liver function. The lack can, of course, be congenital, and it may occur in allergic states. The blood fibrinogen is almost al

ways found diminished in experimental allergy I was not aware this observation had been made in purpura before but I find that Bruhl in Germany reported two cases in 1931 in which there was the same finding

The treatment of this kind of purpura is of course purely problematical. Whatever you do for it might be called simply a stab in the dark. The customary thing is to put the child on a simple nutritious diet, giving plenty of orange juice and all other vitamins and a high proportion of protein, and assuming that recovery will soon follow. I think there is a basis for that assumption for if these purpuras are simply allergic manifestations, and there is a lack of fibrinogen in the more severe forms, that lack at least may be compensated for by the increased protein.

DR. COOLEY—I would like to add a few words, particularly about thrombocytopenic purpura, from our own experience. In the first place, as to splenectomy and when you are going to do it.

The first attack of purpura is the critical attack. It seems to be true, undoubtedly that acute infections may bring on a temporary thrombocytopenic state. When you see a child in his first attack of purpura you always have to realize he may never have another. You do not want to think of extreme therapeutic measures at that time because it may be not only his first, but his last attack.

So it has come to be a rule with us that we will not consider splenectomy in the first attack, unless we are absolutely driven to it. It may not be a chronic condition at all.

Then there is always the question, if the thing does prove to be chronic, or recurrent how important it is to the individual patient—and that is a matter of observation. Performing splenectomy only in emergency cases our luck has been very good. I think, with one exception every case on which we have performed splenectomy so far, has been cured but we have been pretty careful in how we select them. The one case we have not cured was one which we lost just a week or so ago, and it is a good illustration of the complete futility of treatment in some types of thrombocytopenic purpura.

This child came in after a first attack following a glandular infection preceded by measles. She came in bleeding from the mouth and one ear. In the course of her stay in the hospital she developed bleeding from the intestines and kidney. Bleeding from the mouth and ear stopped after several transfusions. We were unable to stop the bleeding from kidney and intestine and we tried everything with one exception (and that is the antivenom) that has been recommended on any apparently logical basis for the treatment of purpura.

The child was less than a year old. She had ten transfusions, about 1700 c.c. of blood.

We finally made up our minds entirely against what would ordinarily be our best judgment, to take the child's spleen out. And we did. It proved to be a very difficult splenectomy. By the way this is a good time to say that splenectomy is not a thing to be undertaken lightly because it is often a very serious operation.

This child's spleen, perhaps 50 per cent larger than normal, was pretty well tucked up under the ribs and difficult to get out. The child died of postoperative shock. If she had survived the operation I do not know whether we should have put a stop to the purpura or not. That is the first splenectomy for purpura we have lost.

We have had a number of patients whom we sent home with instructions that they were to be brought back immediately if they had another attack and at least 50 per cent have never returned. We have had another percentage

that came back with rather minor bleeding so we have felt justified in not doing splenectomy. There has been a rather small number whose spleens we have removed with perfectly good results. We always feel we may get a return of symptoms for one perfectly definite reason, that is, it is perfectly possible that a supernumerary spleen may be overlooked in doing a splenectomy. We all know how rapidly they develop after the principal organ has been removed. I believe if I saw a patient with a recurrence, I should ask the surgeon to reopen the abdomen to make sure there had not been a development of a secondary spleen. We have never had occasion to do that, still I believe it would be a logical thing to do.

We have had some interesting experiences. We have seen two cases in whom bleeding was not readily stopped by transfusion in which it was stopped by one of the biologic anticoagulants, the one we use most often and which is called "thromboplastin." We have had two cases of obstinate nosebleed in thrombocytopenia stopped by that method when transfusion failed. This is quite against what you will ordinarily see in the literature but it is not a common occurrence.

In the allergic type we have also just had our first death. The condition was interesting because I have not seen it reported. This child came in with the ordinary picture of Henoch's purpura, i.e., the peculiar type of abdominal pain, followed a few days later by purpuric skin manifestations, which went through the ordinary course. The child had practically recovered although he still had a few spots on the skin, so we thought we were justified in allowing him to go home. He apparently completely recovered at home but suddenly he developed convulsions and died. The autopsy revealed multiple petechial hemorrhages scattered throughout the brain. That is the first thing of that kind I have seen.

One more thing about the treatment of the allergic type of purpura. While we have never found anything definite, we have felt we got better results from the administration of calcium than from anything else we have done.

DR J. A. BIGLER (CHICAGO)—Is there any relation between the decrease of platelets and the amount of types of hemorrhage you may find?

DR SANFORD—No.

DR BIGLER—The reason I asked is because in certain conditions you may have a marked reduction of platelets, down even to 10,000 and still have no evidence of purpura hemorrhagica. Thrombocytopenic purpura is due to reduction of platelets. Why do not all patients with few platelets bleed?

DR SANFORD—So far as I know, there is no answer. It is just one of those things one cannot explain. Of course, the idea that the condition is due entirely to platelet decrease is not acceptable to everyone. McLean was under the impression there were other factors.

DR BIGLER—It is certainly true that with a marked reduction of platelets, trauma has very little to do with hemorrhages. I do not believe anyone has an explanation for some of the peculiar things one observes. It is true, as you say, that there are patients who have almost no platelets at all and that some of these will go for long periods without any bleeding. There seems to be a good deal of evidence that there must be something aside from the lack of platelets which is related to the purpuric manifestations. There must be something which favors passage of the blood through the vessel walls aside from lack of platelets. The evidence for hypersplenism or hyperactivity of the reticuloendothelial system in thrombocytopenia, I think is pretty good. Here again we think it is possible that the disease is actually a disease of the whole system rather than simply of the spleen, although the spleen, being the main part of the reticuloendothelial

system, is probably the main factor in the production of purpura by the destruction of the platelets. On the other hand, it is possible that under some conditions the rest of the reticuloendothelial system is more active in proportion to the spleen than usual and that might explain the failure of splenectomy in some of the cases where it has been reported—that in those cases, the rest of the reticuloendothelial system tissue was more active proportionately.

All we know definitely is that the condition is obviously connected largely with platelet deficiency and removal of the spleen cures or helps to cure this deficiency. Therefore, we have to lay most of the disease process to the spleen. As to the rest of the process, I think we are still in the dark.

DR SMITH—How said you thought a good many of these cases of purpura simplex were allergic. Have you any idea what food does it? Do you think it is bacterial?

DR SANFORD—It might be.

DR COOLEY—I have known of just one case that gave definite reactions to food.

DR SMITH—We had a little girl who had a rash, and ecchymosis of the skin. A physician had removed a large mass from her neck at one time. The attacks kept recurring and for lack of something better to do I put her on a milk diet and she became much worse. I then removed all milk and she cleared up completely. I put her back on milk and she became worse, but her skin did not react to the milk test.

DR ASHMUN—It has been reported in the literature that the platelet count taken after a meal is raised, sometimes a hundred thousand or more so we should avoid taking platelet counts soon after digestion of food. What is your idea relative to the mechanism of that? Is it due to the fact that the blood is being used in digestion and there is less going to the spleen? What is the process? If we were to treat these patients by diet would it be necessary to use any particular type of protein or just more protein than usual?

DR SANFORD—Kugelmaas from his experiments thought any type of protein had more effect on the platelet formation than other types of food. Whipple found that liver was very efficient in promoting blood regeneration and Mackay in several cases of pernicious anemia, was able to increase the platelets to quite high figures, that is above 400,000 by feeding liver to the patients. This would indicate that the platelet forming tissues participate in the general improvement in hemopoietic activity produced by liver or rather a liver diet.

DR BIGLER—What method of platelet count do you use?

DR SANFORD—I think the sodium citrate method is as easy as any. You can do it quicker than any other way.

DR BIGLER—Is there any such thing as a hyperplatemia?

DR SANFORD—I do not know.

DR COOLEY—There are people who believe there is, that the platelet increases after splenectomy may reach a dangerous point. I have seen some very high platelet counts but I have not seen any unpleasant results from them. There are people who believe they can happen and that there may be a tendency to thrombosis. Of course, a certain number of platelets normally go to pieces in the circulation. They seem to believe, and probably logically that in proportion a greater number will go to pieces when the count is high and there may be

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told her it was probably an angioneurotic edema. A few hours later she brought the child to the office and he was perfectly normal. It recurred on the baby's cheek and lip.

Three days later the child was afebrile and had no temperature. The child later developed temperature 105. Adrenalin was given. I have seen no definite reports of angioneurotic edema in the medulla or thermo-regulating center. I do not know how one could prove this happened but as quickly as we administered adrenalin the temperature went down eight or nine degrees.

Again, after two or three days the child suddenly developed distress in the stomach and the entire upper half of the abdomen became greatly enlarged. The child was in great distress and later about a quart of a chocolate-like material was siphoned off from the stomach which reacted very strongly to blood. This recurred again two days later and on the second occasion the child had some fever. Following this we tested the child for many things from the allergic standpoint except house dust. Results of these tests were negative.

DR OTT—I have not had a case of purpura under my care but certain other conditions like some of the upper respiratory infections have brought out certain points in relation to allergy. In one case of a child I could not get a sample of the respiratory secretion but I took cultures from the stool. I found that the child gave a very good epidermal reaction to these organisms. I then desensitized the patient. The patient had surprisingly good results in a few days. One case is not enough to prove anything but I think it might be a good thing to look at allergy from a bacterial standpoint rather than entirely from a food standpoint.

DR SANFORD—Of course all this subject of purpuras is not clear. What I have given you is simply the usual ideas of the present time. As Dr Gorter said it does not work out nearly so nicely as we like to think that these are all allergic manifestations. There have been a few cases in which work has been done to indicate that it might be that type but on the whole there are just as many cases where it is absolutely impossible to find any reason. I think your suggestion about the bacteriological viewpoint is certainly worth while.

QUESTION—Dr Gorter in the first case you cited of what did the child die?

DR GORTER—It was one of a large group of children. We did not have many autopsies. One might say it is almost a description of leucemia.

DR COOLEY—I have seen several such cases. Some of the writers make quite a point of the fact that one can see all grades between thrombocytopenic purpura and an outspoken aplastic anemia. There is a considerable group in which apparently there is a marrow hypoplasia. I wonder whether that would not apply to the group you are speaking of.

DR GORTER—Yes, I should think so. I think that in most cases of real aplastic anemia it starts so to speak, with acute symptoms and death occurs in six weeks or so with high fever.

DR COOLEY—I think there is a very definite difference between what I speak of as hypoplastic anemia and aplastic anemia. I think sometimes the platelets are more involved than the other blood elements in the hypoplastic state. The pathologic pictures are very different in the bone marrow in the two conditions.

DR SANFORD—In answer to a question about ultraviolet therapy the results are variable sometimes there is an increase. Certainly in the newborn

there will be a slight increase in platelets following ultraviolet radiation but the newborn is most unstable and there is no reason to expect that the adult would react similarly

DR COOLEY—It seems to me the argument for that type of treatment is not very good because in experimental animals we are not dealing with a condition of excessive platelet destruction. The difficulty in thrombocytopenic purpura is that you would not expect to be cured by any temporary or minor increase in platelet production because they are all destroyed. That seems to be true except in some secondary forms of purpura. For instance, where the marrow is crowded out by leucemic infiltration. If the productivity of what marrow is left could be increased, that might help.

Dr Sanford, were you going to say anything about the hemorrhagic disease of the newborn?

Hemorrhagic Disease of the Newborn

DR H N SANFORD—Occasionally, in the newborn somewhere between the second and eighth days of life, we meet with a type of hemorrhage for which there is no clear explanation. The forms for which there is a definite etiology, such as infection, septicemia, trauma and congenital syphilis, have been excluded. Clinically there is nothing particularly characteristic except the bleeding. This may be from the mucous membrane of the nose or gastrointestinal tract, the cord, or the meninges. There are no other symptoms except the secondary anemia. The bleeding rarely comes before the third day, and rarely after the sixth. To judge from reports in the literature, the frequency of this condition must be decreasing rapidly. Le Qneux's statistics, the earliest I know, showed an incidence of nearly 35 per cent. The last series of any note is one from Grob in Lucerne, in which he found only fifty cases in ten years.

As to the cause of the condition, every one of the clotting factors mentioned by Dr Cooley has been reported as being affected. Whipple found a decrease in prothrombin, Schloss and Kommisky found lack of thrombin in one case, and of fibrinogen in another, Kugelmass found decreased fibrinogen. All are agreed that the platelets are not diminished. Grob found no lack of them in any of his cases.

This hemorrhagic state of the newborn must be distinguished from bleeding due to mechanical factors. Bonar found chemical evidence of blood in 30 per cent of stools from one hundred nine newborn babies. An infant may vomit swallowed blood if the mother's nipples are cracked. Hemorrhagic disease is excluded by the absence of any change in bleeding or clotting time. Rodda, in his studies of normal bleeding and clotting time in the newborn (made with capillary blood) found that at birth the infant has times comparable with those of the adult (five or six minutes' clotting and three or four minutes' bleeding time), and that the time tends to increase to a maximum about the fourth day, after which they drop to normal. If this is true, practically every newborn child is in a prehemorrhagic state. Several years ago we determined the clotting factors in a group of thirty-five newborns. We found thrombin and antithrombin a little lower than normal and fibrinogen slightly higher. If this is the rule, there must be other factors at work in the hemorrhagic state. We endeavored to find things which would alter the proportions of the clotting elements. Vioiolet and ultraviolet light had no effect. The first change observed followed withholding protein and fat from the food. This was done by keeping the child from the breast for five days, giving ample salts and carbohydrates. By this procedure we obtained a distinct lessening of fibrinogen, but hardly enough to cause bleeding.

The decrease in this condition seems very striking to me. Since we have been interested in the study of the clotting factors in the last five years we have not had a single case of hemorrhagic disease in which we could make these determinations. We have had two or three brought in from outside but in too advanced a stage.

As to prophylactic treatment, that, of course is an obstetric problem, and I believe the lessened incidence of the disease is due to the fact that most of the mothers' diets are better. We never see it in private practice and most mothers in dispensary groups have a well supervised diet. Moore was able to produce a hemorrhagic condition experimentally by feeding the mother a diet lacking in vitamin B. Graham, in 1910 found that young animals subjected to prolonged anesthesia showed increase in bleeding and clotting time. The same thing has been shown in the child born after a long ether or ethylene anesthesia. As to obstetric manipulations, I have never observed that they had anything to do with producing hemorrhagic disease. Most of the cases have followed normal deliveries. Kugelmass advocates giving gelatin from birth for prophylaxis. Most babies will take gelatin readily, but it seems to me that if one wishes to administer protein, it might as well be in the form of a high protein food that the child can utilize.

In treatment of the actual hemorrhage I think that anything except blood is useless—calcium, viosterol thromboplastin etc., are simply a waste of time. For the past fifteen years immediate injection of whole blood has been recognized as the only effective treatment. Dr. Smith asked about mother's blood in the hemophilic. There is a feeling among obstetricians that they have better results in the hemorrhagic disease from the use of the father's blood instead of the mother's. In the past few years we have tried to determine whether father's blood mother's blood or "foreign" blood has the most effect on the clotting factors. From our figures it would appear that we had somewhat more effect from the foreign blood. Father's blood comes next and the mother's blood gives somewhat the poorest results. In using foreign blood one must of course be sure about the Wassermann test, while one does not have to worry about that so far as the parents' blood is concerned. If there is anything to an inherited or maternal tendency in the disease it might be carried over in the mother's blood. I like to use the father's blood when I can. We have had very good results from giving small quantities (10 c.c.) of father's blood intramuscularly. In severe cases we have given 50 to 100 c.c. intraperitoneally and thought we got as good results as from intravenous injection. We never give large amounts that is necessary only in rare cases. Usually the bleeding can be controlled satisfactorily by small intramuscular injections.

DR. COOLEY—The idea of starting with the small amounts of blood however is a little dangerous but, of course, that has been extensively advocated. Nearly fifteen or twenty years ago it was a general procedure and I saw several cases that made me reach the conclusion I would rather play safe and give more.

QUESTION—Wouldn't it be better to give a transfusion and begin life less anemic?

DR. SANFORD—My feeling is that some of these patients are very anemic. Such a child should have the blood replaced in a very short period of time. It certainly does not do any harm and I think there is everything in favor of it.

QUESTION—What veins do you usually use in the newborn?

DR. COOLEY—If you are particularly expert in manipulation, it is surprising what you can do in some of the smaller veins. I know one man who gives trans-

fusions in the newborn infant in the veins of the scalp but that takes practice. We use the saphenous vein more than any other.

DR ASHMUN—Perhaps you are familiar with Dr Wagner's series in Cincinnati. He had 200 cases of premature infants he reported in which he used the blood as prevention of hemorrhagic disease. He has another 100 cases now making a total of 300 cases. He gives them either the mother's or the father's blood and has not had a hemorrhagic disease develop in any one of those 300.

DR COOLEY—Dr Dunham tells me they have studied a series of 1,000 newborn infants and in that series, where nothing was done for prophylaxis, there were only 3 cases of hemorrhagic disease. She very properly said, it would take a fairly large series of cases to prove results from prophylactic treatment of any kind. In other words, in the series of 300 you cite, you would not have expected more than one case of hemorrhagic disease.

DR ASHMUN—In view of the fact that there is such a small incidence, is it not likely that diet plays a large part?

DR COOLEY—Dr Dunham was asking what I thought they might do to study that question further. She suggested the thing to do was to study the mothers.

DR SMITH—The premature infants would be better to receive the father's blood, according to your findings, Dr Sanford.

DR SANFORD—I do not remember seeing a case of hemorrhagic disease in the premature infant. In fact, we have not had a case on our newborn service of hemorrhagic disease in the last five years. The only cases we have seen are those coming in from the outside.

DR ASHMUN—Do you not think they formerly classed a good many as hemorrhagic disease that were not, or that are not classed that way now?

DR SANFORD—I meant to mention that. You will find a lot of cases of hemorrhagic disease due to syphilis. I think the big point is that the bleeding time is almost always increased over the coagulation time. If it is increased at least five or more minutes over the coagulation time, it is undoubtedly syphilitic.

DR HELMINE JEIDELL (SALT LAKE CITY)—Is it usually found in only one pregnancy?

DR SANFORD—There have been some cases reported where it occurred in more than one pregnancy but I have never seen it.

DR COOLEY—There is one other subject that might be worth speaking about while we are on this question, that is a procedure I suppose to be common—making clotting and bleeding time tests before operations. My opinion is that those things as ordinarily done are not worth anything and yet it gives people a feeling of safety which I do not think is warranted. If that sort of thing is to be done at all that is where this scheme of Kugolmass' of using a clot index is worth something, because it will uncover things not necessarily uncovered by the ordinary tests. When, for one reason or another, one really wants to have a definite idea whether a patient is likely to bleed abnormally after a tonsillectomy or something of that kind, I think the surgeon and the family doctor should understand that something more than just the ordinary coagulation and bleeding time from capillary blood should be used and I do believe this scheme of Kugolmass' has probably a good deal of value.

The meeting adjourned at 4:50 P M.

Academy News

MEETING OF REGION III AMERICAN ACADEMY OF PEDIATRICS

PRESBYTERIAN HOSPITAL, CHICAGO, SEPT 23 1933

(Number present, 28)

Dr H F Helmholtz, Chairman, Presiding

Motion made by Grullee seconded by Gengenbach that an invitation be extended to all members of the disbanded Central States Pediatric Society to attend the clinical meeting of Region III. Carried

There was a discussion of the character of the meetings to be held by the Region in the future.

Grullee gave his opinion that the meeting should be mainly clinical.

Veeder after explaining the type of meetings held in St Louis, suggested a one day clinical meeting by clinicians in the city where the meeting is held one day program given over to papers or presentations by men from other cities in the Region.

Aldrich thought it was wise to determine how many cities in the Region could entertain the meeting.

Rowland states that he always liked to see the interesting cases.

Hamilton especially likes the clinical part of the program.

Irish thinks the important thing is to present practical subjects whether didactic or clinical. He does not think that the demonstration of a patient is always effective in teaching a particular point or subject.

Helmholtz summarized that the meetings should be both practical and clinical, that a local committee be given plenty of latitude to draw on the entire Region for men to present the program.

Moved by Veeder seconded by Gengenbach that the matter be left entirely to the Regional Committee. Carried

Next meeting to be decided by the Regional Committee and Gengenbach suggested that the number of sessions at the time of the meeting is a question to be considered by the Regional Committee.

Veeder expressed the opinion that he would like to have the dinners, such as were held in the Central States Pediatric Meeting continued in the Region.

Aldrich suggested that the clinical meetings be made open meetings.

Grullee thought that the business meeting should be held at the time of the dinner.

Gengenbach suggested that if the meetings be open it would be difficult to get a place big enough to hold the meetings.

Reports of State Chairmen

Hamilton of Nebraska reported that they have organized a committee in Omaha which is advisory to the schools on all health activities. This committee is very active. It is handicapped by having no money to carry on any work. There is no activity outside of Omaha.

Carson of Kansas—no report

Schwartz of Wisconsin—no report

Baxter of Illinois reported that the committee in Illinois has been very active. The chief activities include first, a subcommittee appointed to contact and advise with all governmental departments having to do with Child Welfare and Child Health. This committee has secured the appointment of two members of the Academy on the advisory committee of the Illinois State Department of Health. Second, a subcommittee has contracted with all nongovernmental organizations in child welfare. This committee has made such contacts and is making some progress. Third, the committee has succeeded in the establishment of a Pediatric Section in the Illinois State Society. Fourth, the committee has made a policy to conduct all of its state activities through the channels of the regularly organized State Medical Society. Fifth, the committee has organized statewide pediatric programs, the purpose of which is first, to stimulate the greater interest on the part of the general practitioner in both the well and sick child in order to make the general practitioner more child conscious. Second, it is the ideal that eventually there will be no need of any child welfare organizations because of the desire to make every doctor's office a health center. The state has been divided into districts more or less corresponding to the Councillor districts of the State Medical Society. A chairman has been appointed for each district. Meetings have been arranged for and five meetings have already been held. The reception of these meetings has been most gratifying and encouraging. During the winter it is hoped to put on a similar program in each of the Branch Societies of the Chicago Medical Society.

Hill of Iowa reported that for two successive years, a pediatric program has been put on at the State Society meeting. A committee has been appointed to coordinate with the work of the State Board of Health with the State Medical Society. Education is the object of both of these organizations. Each county is being organized to appoint a committee on Child Welfare and protection. The Iowa State Medical Society maintains a speakers' bureau.

Winters of Indiana stated that they have organized similar to the Illinois state organization. They have a very close contact with the state government and the work is being definitely supported by the Governor.

Gengenbach of Colorado reported that each state has its own problems. They have only five members of the Academy but they have been able to accomplish much through the Rocky Mountain Pediatric Society and by cooperating with the various health departments. The statewide work has been very limited except through some agencies already organized for that purpose.

Helmholz suggested that there may be danger in having pediatric sections of our state societies conduct programs for a few pediatricians and not bring these various subjects to the attention of the general practitioners attending other section meetings. At the Minnesota meeting there are several pediatric papers in each medical program.

Schorer of Kansas City reported that the pediatric club in Kansas City, composed of about 12 pediatricians, has written the entire regulations for contagious diseases and the regulations for immunization which are a part of the municipal health activities, that no clinic of any sort can be started in the county without the approval of the county medical society. This group has also sponsored and regulated the production of milk and they have gotten everything they have asked for from the authorities.

Miner of Michigan—no work has been done. Two meetings have been held.
Carey of Michigan

Hempelmann of Missouri.

Burnham of Ohio had written that they could not be present to report
Meeting adjourned

Region II

Region II of the American Academy of Pediatrics held a meeting on Wednesday November 15, in Richmond Virginia at the time of the annual meeting of the Southern Medical Association. There was a meeting of the Regional Board on Wednesday morning followed in the afternoon by a joint meeting of the health officers of the southern states and the larger cities of the South. This meeting considered the reports from each of the committees appointed last year. Dr. John Rührhah addressed the joint meeting of the members of the Academy and the Pediatric Section of the Southern Medical Association in the evening on 'Acute Anterior Poliomyelitis'.

News and Notes

Dr. Harrold A. Bachmann of Chicago, Attending Pediatrician at St. Luke's and Children's Memorial Hospitals died of heart disease recently at the age of 42 years.

Correction.—Remarks attributed to Dr. Alvah L. Newcomb of Chicago at the Round Table Conference on Rheumatic Heart Disease, on page 611 volume II of the JOURNAL OF PEDIATRICS were made by Dr. John C. McDavid of Oak Park Illinois.

The Central States Pediatric Society held its annual meeting, in Chicago, September 22, 1933. This meeting was held in connection with Region III of the Academy of Pediatrics. Approximately 200 members were present.

The session on Friday morning was held in the new auditorium of the Children's Memorial Hospital. Luncheon was served at the Michael Reese Hospital and in the afternoon a clinical program was presented by the staff of the hospital. Friday evening a dinner was held in Pabst's Cafe at the Chicago Century of Progress Exposition grounds. At this time a business meeting of the Central States Pediatric Society was held. Saturday morning the program was conducted at the University of Illinois College of Medicine.

The business meeting of Region III was held at the Presbyterian Hospital on Saturday afternoon with reports of the various state activities. The problems connected with holding a clinical meeting each fall were discussed.

At the business session of the Central States Pediatric Society the Executive Committee's Report included two recommendations of general interest.

'Recommendation 3. That, whereas there is now a national organization with regional subdivisions i.e., The American Academy of Pediatrics, which to a large extent duplicates the activities so ably carried on for many years by our Society and whereas the Executive Committee at our meeting last year in Kansas City were unanimously of the opinion that the Central States Pediatric Society might well be disbanded but deferred action in order that the question might receive more deliberate consideration, the Executive Committee now recommends that this Society be disbanded.

"It further recommends that the Society suggest to the Regional Committee of Region III of the American Academy of Pediatrics, (1) that its meetings be conducted as nearly as possible after the manner used by our Society in our annual clinical meetings, and (2) that the members of the Central States Pediatric Society in good standing at the time of its disbandment who are not members of the American Academy of Pediatrics, be invited to attend the annual clinical meetings of the regional subdivisions in which they live

"Recommendation 4 That the balance of funds left in the treasury after the obligations of the Society have been paid be transferred to the Abraham Jacobi Memorial Fund, this being a fund under the direction of the Section of Diseases of Children of the American Medical Association to which all members of our Society either belong or are eligible. It further recommends that the president appoint a committee of three to audit the books of the treasurer and that this auditing committee be authorized and directed to turn over the balance after the obligations of the Society are paid, to the Abraham Jacobi Memorial Fund in accordance with the preceding resolution

"All of the recommendations of the Executive Committee except the fourth were approved as read

"The recommendation regarding the disposition of funds was discussed by several members. Dr Veeder proposed that in making the transfer we specify that in order to perpetuate the name of the Society, some of the money be used to make a medal called "The Central States Pediatric Society Medal" to be awarded each year to some one for special excellence in some pediatric work. Dr Helmholtz, Dr Neff and Dr Grulee spoke in favor of this idea

"A motion was made by Dr Grulee and seconded by Dr Helmholtz that the money transferred to the Abraham Jacobi Memorial Fund be specified as the Central States Pediatric Society Fund with the suggestion that part of it be used to perpetuate the name of the Society, the manner in which this is to be done to be decided by the Committee in charge of the Abraham Jacobi Memorial Fund

"This motion was carried

"The original recommendation with this amendment was then approved by the Society"

The annual meeting of the Pediatric Section of the Michigan State Medical Society was held at Grand Rapids, Michigan, on September 13 and 14, 1933

Dr Thomas B Cooley of Detroit gave an interesting résumé of the present day conceptions of Blood Dyscrasias in Infancy. Dr T Wingate Todd presented a résumé of his work on Bone Age in Infancy which is being carried on at the Brush Foundation in Cleveland, Ohio. Dr Louis H Newburgh of Ann Arbor, Michigan, reviewed the recent advances in the study of Calcium Metabolism

The officers elected for the year 1933-34 are as follows

Chairman	W A Collins, M D
	103 W Burdick
	Kalamazoo, Michigan
Secretary	Edgar E Martmer, M D
	749 David Whitney Bldg
	Detroit, Michigan

The next meeting will be held at Battle Creek, Michigan, in September, 1934

The regular meeting of the Detroit Pediatric Society was held September 6 1933, at the Children's Hospital of Michigan

The following officers for the year 1933-34 assumed their duties.

President:	J A Johnston M.D 2700 West Grand Bldg, Detroit.
Vice President	E W May M.D 1551 Woodward Avenue Detroit.
Secretary	Edgar E Martner M.D 740 David Whitney Bldg Detroit.
Treasurer	E. W. Wishrope M.D 3061 Woodward Avenue Detroit

The following appointments have been made to membership in The American Board of Pediatrics.

By the American Pediatric Society
Dr C Anderson Aldrich Winnetka Ill.
Dr Henry F Helmholtz, Rochester Minn.
Dr Phillip Van Ingen, New York.

By the American Academy of Pediatrics
Dr Harold C Stuart Boston, Mass
Dr Borden S Veeder St Louis, Mo
Dr Alfred A Walker, Birmingham Ala.

By the Section on Pediatrics of the A. M. A.
Dr Wilburt C Davison, Durham, N. C.
Dr Franklin P Gengenbach, Denver Colo
Dr Edward B Shaw San Francisco Calif

The Board is in the process of organization and incorporation. Announcements in regard to the Board will appear in *The Journal of Pediatrics* and *The American Journal of Diseases of Children*.

Book Reviews

The Diagnosis and Treatment of Postural Defects. W M Phelps and R J H Kipphn, Charles C Thomas, Springfield, 1932, pp 180

This monograph is the best one on the diagnosis and treatment of postural defects that has come to my notice. The material as well as the manner in which it is presented and illustrated leaves nothing to be desired. It can be recommended to all students of the subject and the knowledge contained in it should have far wider application especially in the physical education departments of our schools. If only teachers of physical education realize that—

- (1) The term "flatfoot" is very misleading,
- (2) That forward shoulders in children is related to the prominent abdomen and is rare during the adolescent period,
- (3) That there should be no attempt to localize lumbar correction in children because of the danger of compensatory defects due to flexibility, much wasted effort as well as considerable harm would be prevented.

Chapter I on evolutionary influences will repay anyone for careful study. While one must, as the authors frankly admit they have done, draw upon his faculty for imagination when he attempts to understand the many and varied steps by which man has arrived at his present development of the upright posture with bipedal locomotion, there is no other method of analysis which so satisfactorily serves as a basis for study and didactic teaching. The reconstruction of evolutionary influences with the realization that gravity is the principal force in the maintenance of good posture with a minimum expenditure of muscular energy lay the best foundation for more detailed study and a clearer understanding of body mechanics.

On the subject of environmental influence I cannot entirely agree with all the ideas expressed by the authors. The study of this chapter gave me the idea, perhaps mistakenly, that the authors have not studied the natural changes in posture that one sees in the observation of individual children during the whole period from infancy to young adult life. While the study of many individuals in age groups yields invaluable information, it is only by the continuous observation of individuals as each grows up that one learns to predict his future development. Such study is the basis for the following suggestions.

Every normal infant is bow legged until after he has walked for a few months. The authors suggest too early walking as a cause of bowlegs. All children go through a period of physiologic knock knee with pronation of the feet accompanied by a stretching of, or a lack of development of the heel cords which permits dorsal flexion of the feet well beyond a right angle. This stage of knock knee and pronation of the feet reaches its height at age three and is sufficiently corrected by age five or six to be of no consequence. The correction is accomplished, I think, by the development and better coordinated use of the external rotators of the thighs and of the gluteals. The authors mention both the pronation of the feet and the knock knee but do not sufficiently emphasize them as parts of normal development. Failure to recognize the physiologic nature of the normal amount of pronation in the feet of young children has given rise to the widespread practice of attempting to correct it by means of advancing and elevating the inner borders of shoe heels (Thomas heels) and worse still by elevation of the inner borders of the sole as well. These mistaken attempts at cor

rection contribute considerably to the unnatural shortening of heel cords and very probably to the development of rigid contracted feet. In turn this shortening of the heel cords contributes the undesirable effects higher up so well described by the authors on page 15. When the child is about six years old if pronation persists, it may be easily corrected because the child will then have lost some of his natural flexibility as well as have acquired such a degree of muscular development and general coordination that he can better distribute and utilize the effect of the correction. This argument is in line with the authors well-defined and wise warning that posture training should not be begun too early in the child's life because of the danger of overdevelopment of certain muscle groups.

The importance of shoes and stockings is well emphasized. Anyone who has observed the deformities produced by tight stockings and badly fitted shoes, especially the shoes that are fitted or worn until they are too short, can have no doubts concerning the attention that should be given to these articles of apparel. I cannot agree with the authors' idea that 'a moccasin is innocuous when worn on a normal foot'. A moccasin is I am certain the only form of shoe for normal infants until the full development of skillful coordinated walking which does interfere with the best development of the muscular power and functional skill of the feet. Why should the feet only be set aside as the part of the body to which support should be applied as a preventive measure? The advisability of support for the feet depends upon the individual case just as the authors point out in discussing shoulder braces and abdominal supports in another paragraph.

The authors' conclusion 'the environment factors in the posture of the well pre-school child are therefore confined chiefly to the feet' if accepted literally will produce in one's mind a conception of body mechanics which is not in accordance with physiologic facts. The feet are only part of the whole mechanics of the body concerned in bipedal stance and locomotion. An imbalance produced by deformity of the feet must be counterbalanced by a deformity or at least a deviation in the opposite direction in some other part of the body. Conversely a deformity or deviation in some other part of the body may have its opposite compensating or balancing deformity in the feet. Correction of the foot deformity if properly done will have a beneficial effect on the general body mechanics. However if the foot condition is thought of too exclusively of its relationship to the rest of the body harmful overcorrection may result.

CLIFFORD SWEET

The Early History of The Infant Welfare Movement. G. F. McCleary. London 1933. H. K. Lewis & Co. pp. 178

An interesting and readable account of the origins of the Infant Welfare Movement. While dealing chiefly with the movement in England, the discussion of the French influence is adequately covered. The author stresses the importance of the early work of Dr. Nathan Strauss and Dr. Henry L. Colt in America and the emphasis placed upon milk. We recommend the reading of the book by the younger pediatricians who step into work in the fully developed welfare center of today.

BORDEN VREDEL.

Therapeutique Hydro climatologique en Pédiatrie P Nobécourt and G Boulanger Pilet Paris Masson et Cie, 1933, pp 195

A discussion of the indications for hydrotherapy and climate in various conditions in infancy and childhood A list of the principal thermal and climatic stations in France is given

B S V

The Clinical Study and Treatment of Sick Children. John Thomson and Leonard Findlay Edinburgh Oliver and Boyd, 1933, pp 1075

A fifth edition of Dr Thomson's well known textbook by Dr Findlay The revision is excellent and in keeping with the high standard set by Dr Thomson in the first edition some thirty five years ago

B S V

Comments

FROM reports we have heard and a reading of the minutes of the recent Child Health Recovery Conference called by the "Children's Bureau" and held in Washington on October 6 the impression is formed that the gun was fired at the stars to shoot the rabbit on the ground. It is quite obvious to the interested observer that some one became quite excited over the fact that many children in the present period of economic distress and privation were not getting sufficient food to keep them in good health and to prevent being hungry. Therefore, something should and must be done about it. Whether or not one can disagree. It is a question of necessary relief.

The proposition that was outlined and a group called to Washington to adopt was a nationwide examination program for malnutrition, this to be carried out by the respective states under the general guidance of the Children's Bureau. This is quite a different matter. The last error, of course lies in thinking of malnutrition and insufficient food as one and the same thing. That insufficient food may lead to malnutrition if continued for a long period is, of course, a fact. Up to the present time at least insufficient food has been one of the more rare and uncommon causes of malnutrition. Where food has been a factor in malnutrition, it has been associated with faulty feeding habits, unbalanced diet and the like rather than with a lack of food. The common causes of malnutrition are found chiefly in disease, physical defects, fatigue and faulty habit formation.

It should not be difficult through our regular social agencies who are handling relief, to find those children who actually are getting too little food. Give them the food. Do it rapidly and at once. But to red tape this around 'malnutrition' and elaborate medical examination in blanks furnished by the Children's Bureau is shooting rather wildly into the air.

What, it may seriously be asked, does the government propose to do? If malnutrition is the goal, does the government intend to provide convalescent homes for the thousands of malnourished children with an underlying cardiac or tuberculous lesion, or bloody holidays when tonsils and adenoids are removed by the thousands? If 'malnutrition' as shown by a medical examination is the basis for giving extra food to hungry children who need it the only logical thing is for the government to provide relief for children malnourished from other causes. It is rather an absurd situation.

From a more practical standpoint as physicians we must ask first of all what standards are to be used. It has taken years and will continue to take years to overcome the misuse and misapplication of height weight age tables of measurement as applied to malnutrition. This if we recall it correctly was largely the result of the measuring and weighing campaign of the Children's Bureau. There is danger of 'food and malnutrition' being linked together in the minds of the laity as one and the same thing if a 'malnutrition' campaign on the basis outlined is made a propaganda movement by the Children's Bureau.

We are strongly in favor of food relief for children who need it. We are further in favor of the careful medical study of malnourished children and the application

of indicated remedial measures. This latter is a time taking process and a continuous need, and one which is under way in many of our cities and in some of our states. For example, the work in Pennsylvania was outlined by Dr. Hamill in his recent presidential address in the September number of the Journal. We feel, however, that the conference in Washington exhibited a lot of loose thinking and mixed up some simple direct things in a complicated unnecessary way.

This is an expression of personal reaction and opinion. Doubtless, many will disagree. This column, as has been stated several times, is an open forum for the discussion of pediatric subjects and is open to those who hold opinions which differ. Quite obviously with such a purpose in view, it cannot be regarded as the "official voice" of the Academy of Pediatrics. Academy discussions and actions are printed under the head of Academy Proceedings.

BEGINNING with the January number, the Journal will make a past to present change. The interesting series of eighteen articles on Pediatric Antiques by Dr. Drake of Toronto will end with the present number. In January the first of a series of articles on "American Pediatric Clinics" will appear. Twelve outstanding clinics have been selected by the Editorial Board. Although there has been some objection on the score of "modesty," the Journal has requested that the individual clinics be described by the Chief of Staff or someone who has been intimately connected with the clinic for a number of years rather than by an outside reporter. The scope of the articles will include the history and aims of the clinic, physical and clinical facilities, house officers, and research facilities. If the series is as interesting as the Editorial Board expects, it will be followed by one on foreign pediatric centers. The Editors wish to take this opportunity to express their thanks to Dr. Drake for the time and study he has given to the series of special articles closing with this number.

WE WELCOME the first number of the *Indian Journal of Pediatrics*, published in Calcutta. The Journal, which is to appear quarterly, is published in English and is edited by K. C. Chaudhuri. The first number contains a foreword by Sir Nilratan Sircar, a Birthday Greeting by Dr. Robert Hutchinson, and an Introduction by Czerny. The contents contain several original articles, society proceedings, book reviews and abstracts. May it live and prosper.

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VOLUME III

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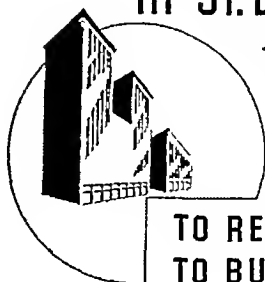
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By Floyd Eddy Hogeboom, D.D.S., Professor of Children's Dentistry, College of Dentistry, University of Southern California Former Member of Health and Development Dept., Pasadena City Schools Former Member of Children's Hospital Staff, Los Angeles Consultant to Orthopaedic Hospital, Los Angeles Third edition, revised and enlarged 350 pages, with 249 illustrations Price, cloth \$6 50

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The Journal of Pediatrics

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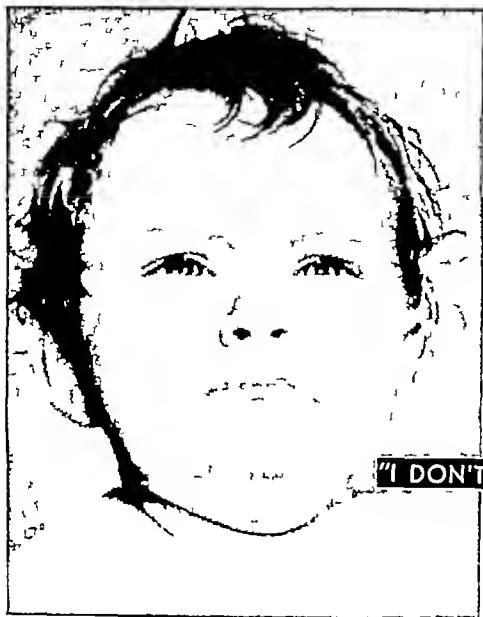
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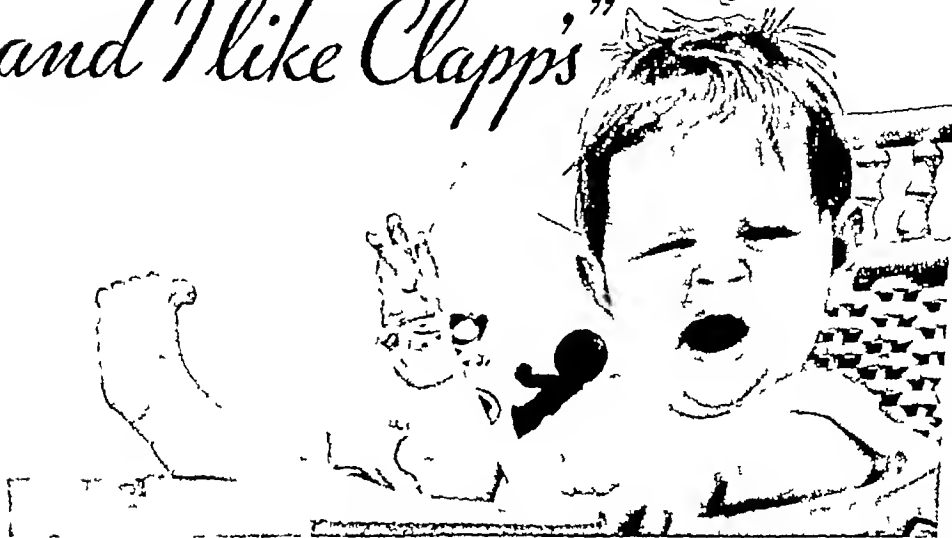
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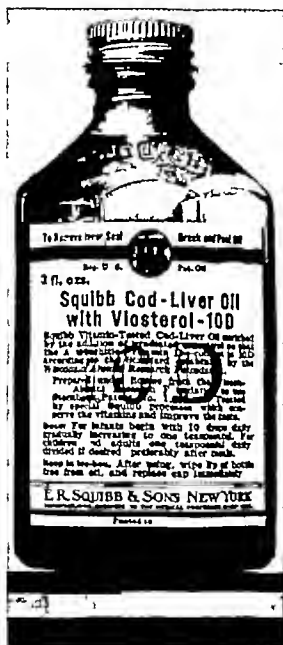
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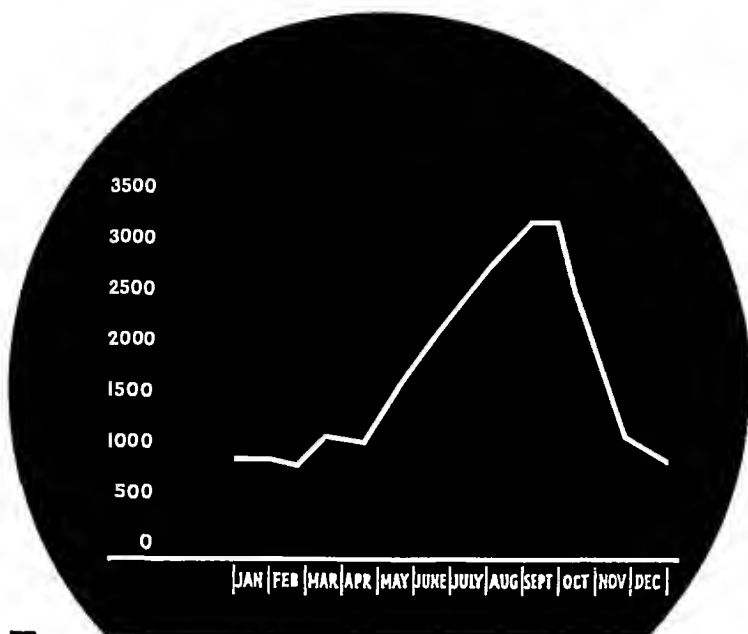
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Test these tablets in practice and note the greater protection against rickets, the more rapid improvement in weight, the better clinical results wherever you would prescribe Cod Liver Oil

Literature and Samples on request

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Yes please Samples and special bulletin on
McKesson's Vitamin tablets

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CAL-BIS-MA

A TEASPOONFUL by the measure—three minutes by the clock, is the efficiency story of Cal-Bis-Ma in gastric neutralization. Sodium bicarbonate and magnesium carbonate for quick neutralization, calcium carbonate and bismuth for prolonged action.

And, in addition, *colloidal kaolin* to supplement the bismuth salts for soothing and protecting the irritated mucous membrane, and to adsorb gases that may form in the stomach. Well adapted for the alkaline treatment of gastric ulcer.

In nausea of pregnancy exceptionally good reports are being received.

WE WILL GLADLY SEND A
COMPLIMENTARY TRIAL SUPPLY

WILLIAM R. WARNER & CO. INC.

113 WEST 18TH STREET, NEW YORK CITY

Almost as Simple as Breast Milk



SUGGESTED FEEDING TABLE

Age	Time	Amount	Time	Amount	Time	Amount
3 days	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
4 days	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
5 days	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
6 days	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
7 days	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
2 weeks	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
3 weeks	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
4 weeks	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
5 weeks	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
6 weeks	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
2 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
3 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
4 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
5 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
6 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
7 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
8 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
9 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
10 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
11 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz
12 months	1 to 2	1/2 oz	3 to 4	1/2 oz	5 to 6	1/2 oz

* These quantities refer to fluid ounces of S. M. A. diluted according to directions. At this age it is customary to add soups and vegetables to the diet especially spinach.

TIME SCHEDULE
2 feedings 6 9 12 3 6 9 and once during night.
3 feedings 6 9 12 3 6 9 and 12
4 feedings 6 9 12 3 6 9 and 12
5 feedings 6 9 12 3 6 9 and 12

NUMBER OF FEEDINGS IN 24 HOURS.
The number of feedings should be the same for infants and not for adults.

HOW TO PREPARE



THE POWDERED FORM



+



=



To each measure of S. M. A. ADD One ounce of boiled water = One fluid ounce of S. M. A. ready to feed.

To prepare a two ounce feeding fill the cup twice and add two ounces of water. One fluid ounce S. M. A. diluted according to directions is equivalent to 20 calories.

THE CONCENTRATED LIQUID FORM



Shake thoroughly pour the contents of one quart (1 qt.) of milk bottle or 32 oz. glass.



Full the bottle to the top or divide the quart of prepared S. M. A. into 32 equal feedings and keep on ice or in a cool place.

NO ADDITIONAL COD LIVER OIL IS NECESSARY

It is NOT necessary to give cod liver oil with S. M. A. as it contains an adequate amount to prevent rickets and osteomalacia. The kind of food requirements and their variations in S. M. A. also play a role in the prevention of rickets and osteomalacia. CHOLERA LIVER, of course, should be given the infant fed on S. M. A. just as it is in the present practice to give it to breast fed infants.



NO complicated feeding calculators are necessary in feeding S. M. A., the anti-rachitic breast milk adaptation.

As with breast milk, the total quantity of S. M. A. is merely increased as the infant's requirements increase with age.

For the convenience of the busy physician we have prepared the simple suggested feeding table shown above. On the other side are brief directions for the preparation of S. M. A. and suggestions on the amounts to be fed.

FREE! Send the coupon for your copy of this single thickness celluloid card, 2 1/4 x 4 1/2" with rounded corners to go into the pocket readily.

S. M. A. Corporation 50-03
4614 Prospect Avenue Cleveland Ohio

Please send me without charge or obligation.

- ☐ Celluloid feeding card
- ☐ Trial Supply of S. M. A.
- ☐ Direction folder a table for physician to give mother

Attach coupon to your D. blank or letterhead



Unseasoned

Specially Prepared

The Gerber Products—strained vegetables and strained cereal—are prepared without the addition of salt, sugar or other seasoning

values are also conserved by the use of vacuum pans in reducing Gerber Products to proper consistency

With these Gerber advantages the physician can always be certain that his feeding prescription represents maximum values and can be followed accurately and intelligently in the home

A Suggestion to Physicians

If, like thousands of other physicians, you are advising the use of Gerber Products, may we make this suggestion? Tell your adult patients that the Gerber Products are unseasoned Adult tastes—educated to seasoned foods—cannot appreciate the significance of the unseasoned flavor in Gerber's without an explanation

If you have not already examined samples of Gerber's Strained Vegetables and Gerber's Strained Cereal, fill out and mail the coupon below

Strained Beans
—Carrots—Peas
—Green Beans—
—Spinach—
—Vegetable Soup
—Tomatoes—
4½ oz. cans
Strained Cereal
10¼ oz. cans

We take the liberty of again calling this important Gerber feature to the attention of physicians because it emphasizes the fact that the Gerber products are—in every detail—specially prepared strained foods. These products are not merely the ordinary canned foods of commerce—seasoned to suit adult taste, and then strained and re-packed for infant or special diet use. Instead, the Gerber Products are the development of years of laboratory work, clinical work, hospital work, and the findings of two University Fellowships established to determine the ideal requirements for strained foods

The Gerber Products are not only unseasoned but more important, they are prepared by special processes and special machinery that exclude oxygen in cooking and straining operations providing optimum vitamin retention. Mineral salt



15c at
Grocers and
Druggists

Gerber's 9 STRAINED FOODS for Baby

GERBER PRODUCTS COMPANY, FREMONT, MICHIGAN
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☐ You may send me a sample of Gerber's Strained Cereal and Gerber's Strained Vegetables—also analysis and description of these products as filed for acceptance with the Foods Committee of the American Medical Association.

☐ Booklet, Baby's Vegetables and Some Notes on Mealtime Psychology

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Why CARITOL?

- 1 For ages, man has eaten certain palatable fruits, vegetables and dairy products to satisfy his hunger
- 2 His body requirements for vitamin A were thus unconsciously satisfied in greater or less degree
- 3 The substance responsible for this vitamin A activity has recently been shown to be carotene, a yellow organic pigment [$C_{40}H_{56}$] called Primary Vitamin A by Sherman & Smith in 1930
- 4 The prevalence of latent vitamin A deficiency diseases suggests to numerous investigators that modern diets do not contain enough carotene to fully satisfy the requirements of many individuals.
- 5 The fact that carotene is normally present in various parts of the body such as the spleen blood lymph breast milk, corpus luteum, placenta, ovaries, suprarenal glands and bone marrow would seem to indicate that in addition to its activity as a vitamin, carotene itself meets other body requirements besides its conversion into the colorless product by the liver
- 6 If this deficiency is to be made up, what is more natural than to supply the same palatable substance carotene, derived from vegetables, in concentrated form?
- 7 This is now possible. A highly potent solution containing 0.3% carotene [Primary Vitamin A] in oil is offered to physicians as Smaco Caritol, available at most pharmacies.
- 8 Caritol literature may be obtained from S. M. A. Corporation, Cleveland, Ohio.



Information about Karo Syrup

Which Will Interest All

Physicians —

Particularly Pediatricists

In response to numerous requests from physicians, Corn Products Refining Company is pleased to publish the following analytical data about Karo Syrup (Blue Label)—which has proved so effective in the feeding of infants

The following acceptance of Karo (Blue Label) by the committee on foods, appeared in Journal of the American Medical Association, January 23rd, 1932

The product is a mixture of corn syrup with a relatively small amount of refiners' syrup. The refiners' syrup must be acceptable in flavor and color and fulfil the U S Department of Agriculture standard for that product, "Refiners' Syrup, treacle, is the residual liquid product obtained in the process of refining raw sugars, and contains not more than 25 per cent of water and not more than 8 per cent of ash."

The corn syrup is manufactured by hydrolysis of high grade corn starch in

dilute hydrochloric acid suspension. The mixture is heated under steam pressure until chemical tests indicate the desired degree of hydrolysis. The resultant mixture is almost completely neutralized with sodium bicarbonate and filtered through white linen filter cloth, the filtrate is passed through a deep bed of animal charcoal for decolorization and deodorization. The final filtrate, which is water clear and odorless, is concentrated under reduced pressure to a density of 1.38 (20 C / 20 C)

CHEMICAL COMPOSITION

	per cent
Moisture	25.3
Ash	0.6
Fat (ether extract)	0.0
Protein (N x 6.25)	0.2
Dextrins* (by difference)	37.1
Maltose (method of Wesener and Teller J Indust & Engin Chem 7: 1009 1916)	22.2
Dextrose (method of Wesener and Teller J Indust & Engin Chem 7: 1009 1916)	7.5
Sucrose	4.8
Invert Sugar	2.3
Titratable acidity as HCl	0.025

CORN PRODUCTS REFINING CO.
17 Battery Place New York





RAPIDLY GAINING FAVOR

ALERDEX - THE PROTEIN-FREE MALTOSSE AND DEXTRINS

WHY IS ALERDEX PROTEIN-FREE?

• Since certain proteins are frequently the cause of eczemas and other forms of allergy it is desirable to eliminate these offending proteins from the infant diet. Cereal proteins are frequently present as contaminants in some milk modifiers. The routine use of a protein free carbohydrate in all milk modifications should help to diminish the incidence of these troublesome eczemas. Alerdex is a protein free carbohydrate developed by our Research Division to meet this need and the demand for it is steadily increasing.

A modest announcement of Alerdex a year ago found physicians ready and anxious for such a product. There is now a definite trend to use Alerdex routinely in all milk formulas.

Of course Alerdex should always be used as the carbohydrate addition with Smaco Hypo Allergic Milks with the assurance that eczemas due to cereal protein sensitization will not be aggravated.

CHARACTERISTICS OF ALERDEX

1. Helps prevent eczemas when used routinely due to absence of offending protein.
2. Use present formulas because Alerdex has same caloric value and percentage of maltosse and dextrins.
3. Does not cake on exposure to air because it is non-hygroscopic.
4. Dissolves readily in warm water or milk.
5. Snow white, free-flowing powder.
6. Inexpensive—in spite of extra processing under technical control, costs no more.

APPROXIMATE ANALYSIS OF ALERDEX

Alerdex is essentially a mixture of approximately equal parts of maltosse and dextrins. It is prepared by a new thermally-destilled process of the enzyme hydrolysis of non-cereal starch, as a result of which it contains no protein contaminant.

Maltosse	30
Ash	0.5
Fat (ether extract)	0.0
Hydrolyzed protein (N x 6.25)	0.05
Reducing sugar as maltose	50.0
Dextrin (by difference)	49.8
Level tablespoons, per ounce	4
Calories per level tablespoon	27½
Calories, per ounce	110



Prescribe Alerdex in your own practice. For samples and literature simply attach this paragraph to your letterhead or prescription blank. S.M.A. Corporation, 4614 Prospect Avenue, Cleveland, Ohio 55-93

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PRESCRIBE ALERDEX THE PROTEIN-FREE MALTOSSE AND DEXTRINS

Effective LAXATIVE MEDICATION

Sodium Glycocholate..... $\frac{1}{4}$ gr
 Sodium Taurocholate..... $\frac{1}{4}$ gr
 Phenolphthalein..... $\frac{1}{2}$ gr
 Extract Cascara..... $\frac{1}{2}$ gr
 Aloin..... $\frac{1}{8}$ gr

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Oxiphen Tablets are particularly useful in habitual constipation because they produce gentle, yet effective laxative action throughout the intestinal tract, stimulating activity of both the secretory organs and the intestinal musculature. They may be used over extended periods without losing their

effect, and without an increase in dosage and, as normal function is re-established, the dosage may be gradually withdrawn without a return of the condition. The formula contains no toxic drugs, and does not produce the "cathartic habit."

The Oxiphen formula combines the hepatic stimulant and chologogue action of the bile salts ("the only reliable chologogue known"—Cushny) with the tonic laxative effect of cascara, the simple laxative action of phenolphthalein and the stimulant action of aloin on the colon. Kindly use the coupon for literature and clinical sample.

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Indianapolis

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(JP 9-33)

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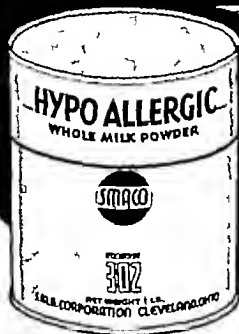
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ALLERGIC MANIFESTATIONS AND HYPO-ALLERGIC WHOLE MILK



Allergic manifestations caused by food may take any of the following forms

- ECZEMA, especially in infants caused by ordinary milk.
- GASTRO ENTERIC DISTURBANCES, as vomiting, diarrhea constipation
- HYPERACUTE TYPE with urticaria, asthma and symptoms of shock.
- BRONCHIAL ASTHMA.
- URTICARIA.
- ANGIONEUROTIC EDEMA.
- ERYTHEMA MULTIFORME

Where milk protein is responsible for such disturbances physicians have reported excellent results from the use of Smaco Hypo-Allergic Whole Milk prepared from tuberculin tested cows milk which is given thermal treatment equivalent to refluxing

Smaco Hypo-Allergic Whole Milk is well tolerated in many cases and can be used in definitely as the processing does not remove any essential food element from the milk the constituent amino acids are still present in the same proportions as before.



The milk thus rendered less allergic is then spray-dried in special equipment and packed in one pound containers in an atmosphere of inert gas (nitrogen). The cost of the powder is 25% less than the liquid form

CHARACTERISTICS of Powdered Hypo-Allergic Whole Milk (Smaco 302)

Helps prevent eczema in patients hypersensitive to milk protein

Can be used indefinitely because all essential food elements of milk are still present.

Use present formulas since this is real cows milk, not a substitute.

Convenience Individual feedings may be made up for infants.

Lower cost Powder form costs 25% less than liquid

Spray dried in equipment reserved for Hypo-Allergic Milk and Alerdex.

It keeps. Hermetically sealed in an atmosphere of inert gas (nitrogen) to prevent deterioration.

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Research Division
of S.M.A. Corporation
Cleveland
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A POPULAR PAMPHLET

This twenty-two page booklet has proven popular with the medical profession. It contains a brief resume of current literature on Milk Allergy, quoting fifty-one authorities prepared especially for Physicians. Send the coupon for a complimentary copy of the fifth edition.

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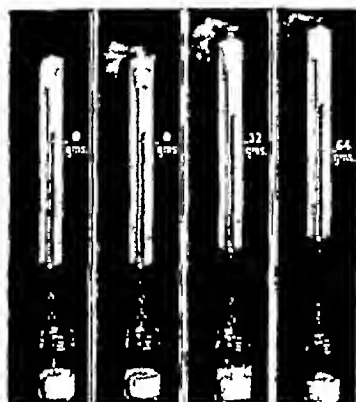
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30-03 ☐ Milk Allergy booklet with bibliography
(simply attach to prescription blank or letterhead.)

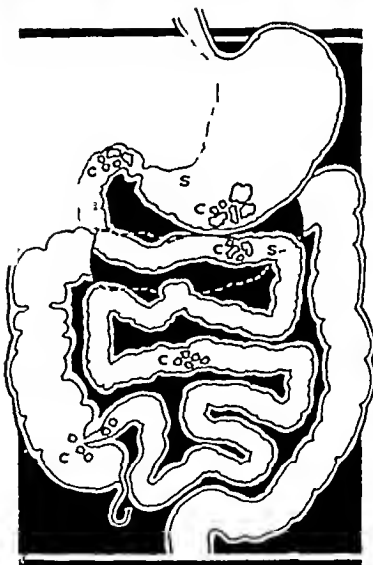
CURD TENSION

- AND INFANT FEEDING -

ITS • EFFECT • UPON • THE • ASSIMILATION • OF
PROTEINS



BREAST MILK SIMILAC POWDERED MILK COW'S MILK



C—Cow's milk S—Similac
Schematic drawing of the relative size of the curds of cow's milk and Similac vomited by six weeks old puppies after one half hour's ingestion.

"THE most available and the most easily digestible form of protein for infants is the protein of milk. The protein of breast milk is more digestible than that of cow's milk."

"In the light of our present knowledge, the chief cause of the difference in the digestibility of the protein of human milk and that of cow's milk lies in the greater proportion of casein in cow's milk"

"It is the formation of large curds which renders the casein of cow's milk so much more difficult of digestion by the infant than that of human milk. If the formation of large casein curds in the stomach can be prevented, the casein of cow's milk is easily digested"¹

In SIMILAC the large casein curds are not formed. The curds formed when the gastric enzymes act upon SIMILAC are small and flocculent, registering zero on the tensiometer, as shown in the illustration, hence more easily digested

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes. Result . . . a more complete utilization of the food elements

¹Morse and Talbott, Diseases of Nutrition and Infant Feeding, pgs 214, 215

Samples and literature will be sent on receipt of your prescription blank

SIMILAC—Made from fresh skim milk (casein modified); with added lactose salts milk fat and vegetable and cod liver oils



M & R
DIETETIC LABORATORIES, INC.,
COLUMBUS, OHIO.

CURD TENSION

- AND INFANT FEEDING -

ITS EFFECT UPON THE ASSIMILATION OF
SALTS



BREAST MILK SIMILAC POWDERED MILK COW'S MILK



C—Cow milk S—Similac
Schematic drawing of the relative size of the curds of cow milk and Similac varied by six weeks old puppies after one-half hour's digestion.

THE mineral salts play a very complicated part in digestion because they are not only absorbed by the intestines but also may be re-excreted into the digestive canal.^{1,2}

"The mineral salts are of even greater importance in infancy than in later life because of the rapid growth of the bony structure. The salts are also necessary for cell growth and are important constituents of the blood and digestive juices, facilitating secretion, absorption and excretion."¹

Some of the important mineral salts are encased within the large tough curds formed from cow's milk, and only those salts that are not encased in the curds are available for metabolism.

The curds formed from SIMILAC are small and flocculent, registering zero on the tensiometer as shown in illustration, hence the mineral salts of SIMILAC are available for metabolism.

The salts of the cow's milk used in the preparation of SIMILAC are rearranged, particularly with reference to calcium, sodium, and potassium as well as phosphorus and chlorine. SIMILAC has a salt balance that cannot be obtained in the ordinary milk dilutions or modifications as made in the home or laboratory.

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes. Result—a more complete utilization of the food elements.

Morse and Talbot: *Diseases of Nutrition and Infant Feeding*, pg. 59
² Marriott: *Infant Nutrition*, pg. 62

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SIMILAC—Made from fresh skim milk (casein modified); with added lactose, salts, milk fat and vegetable and cod liver oils.



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A pentavalent arsenic preparation used in the treatment of various protozoal infections. In congenital syphilis and in amebiasis Stovarsol is administered orally in tablet form, while in the treatment of trichomonas vaginitis Stovarsol powder is employed by insufflation. For clinical reports on the use of Stovarsol in these diseases fill in the attached coupon and send same to

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just what you ordered, except...

HIS mother has measured out the Evaporated Milk water *everything* just as your formula said. Yet

Is that the brand of Evaporated Milk you would have chosen?

When you wrote Evaporated Milk into that formula, you had in mind a grade that would meet your high standards of quality. But the average mother, lacking such standards, chooses on the basis of lay opinion only.

In the matter of brand choice, she needs your professional advice.

Among the brands of Evaporated Milk that a physician can recommend unreservedly for infant feeding are those produced by The Borden Company. For seventy-five years Borden has maintained the highest standards of milk selection and the most rigid requirements throughout the process of manufacture. These standards

and requirements prevail today in the production of all the Borden brands: Borden's Evaporated Milk, Pearl, Maricopa, Oregon, St. Charles, Silver Cow. All are accepted by the American Medical Association Committee on Foods.

Write for free sample of Borden's Evaporated Milk and scientific literature. Address: The Borden Company, Dept. 553, 350 Madison Avenue, New York, N. Y.



The Borden Company was the first to submit evaporated milk for acceptance by the Committee on Foods of the American Medical Association. Borden's was the first evaporated milk to receive the seal of acceptance of this Committee.

Borden's
EVAPORATED MILK

In the Successful Treatment of

MUCOUS COLITIS

Where Diarrhea is either continuous or intermittent, and as many as 20 to 30 stools daily may be passed—stools which always contain the pathologic triad of feces, that is, blood, mucus and pus, and frequently consist almost entirely of this material—

Where Varying With Severity, the condition may grow progressively worse to debility and emaciation, with progressive anemia and irregular periods of pyrexia and where death from the condition is not at all infrequent—

An Eminent Authority Has Found that infants require but little feeding during the acute stage after which he puts the baby on DRYCO

"I put the baby on small quantities of Dryco, full strength, and gradually increased the amount of each feeding as the child improved and could take more. No vomiting occurred after the dextrose and buffer salts were given. With three days of Dryco feeding, the stools became of a normal consistency and were free of mucus. The appetite rapidly returned" (*Arch Pediat*, Vol. XLIX, No 2, Feb., 1932)

DRYCO is digested and assimilated when other foods fail and because of the added vitamin D content, babies receive automatic protection against Rickets, the most common nutritional disease of infancy and childhood

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the cost of a \$5,000 00—\$25 00 accident policy has never exceeded \$13 00 per year

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Patients like to see their meals come when they include junket. This cool, tempting, custard-like dessert never becomes monotonous. It builds appetite for other foods as well. Provides full nutritive value of milk. Easily digested because it contains the enzyme rennin.

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Junket Powder in 6 tempt-
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This authoritative book
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Because it is derived entirely from milk, this calcium is of a most assimilable type, especially useful in periods of growth. Prescribe P M C—one tablespoon three or four times a day—where a high calcium diet is needed and observe the results.



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Dental Clinic Calcium Fixation Diet



The Nursing Mother



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Of course, P M C is not only a *calcium* source. Derived wholly from milk, P M C contains the other essential salts of that "most nearly perfect food." Its full composition is lactose, non-casein soluble milk protein and chlorides, phosphates and citrates of potassium, calcium, sodium and magnesium. The higher concentration of lactose and milk minerals in P M C suggests its definite use as a special dietary food where the child's mineral intake is insufficient—3 tablespoons give approximately 1 gram calcium.

P M C is not just "dried milk" for ordinary milk feeding

Protein Mineral Company, Inc. 18 East 41st Street New York City J P 0

Please send me literature and trial jar of P M C

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DOCTOR, for Your Assistance In Guiding Growth of Baby Feet

has been prepared a Portfolio in which is summarized the latest information on the subject of proper shoes for babies to four years of age. It is a

Synopsis of Baby Shoe Research

in which the Department of Medical Co-operation has assembled in convenient form for constant reference, what Research has developed in recent years. References are quoted

Illustrated with reproductions of X-ray photographs and studies, it contains information about shoes which are designed to aid the profession in preventing improper foot developments

This Portfolio will be mailed without charge to members of the profession upon request. Just write on your letterhead or prescription blank to

Department of Medical Co-operation

MRS. DAY'S IDEAL BABY SHOE COMPANY
DANVERS MASS

MALTINE WITH MINERAL OIL and CASCARA SAGRADA

A Mineral Oil and Cascara Sagrada Emulsion with a

Lessened Tendency to Leakage

WHILE regarded by the medical profession as a valuable intestinal lubricant, mineral oil has certain disagreeable features—notably the tendency to rectal leakage—which limits its use.

More than a year ago tests were begun in the Maltine research laboratories to evolve an effective emulsion which would retain the advantages of the mineral oil and at the same time eliminate the objectionable features. MALTINE WITH MINERAL OIL and Cascara Sagrada is the result.

This mineral oil is incorporated with the Maltine by a special vacuum process by which the mineral oil is broken up into very minute particles. Laboratory and clinical tests covering a period of many months have shown that this combination is superior to the plain mineral oil in taste and appearance. The tests also indicate that the new emulsion lessens the tendency to leakage because of the finely divided nature of the oil present and the small dosage required.

MALTINE WITH MINERAL OIL and Cascara Sagrada is composed of 60% by volume of Maltine (which supplies vitamins B and G) and 40% by volume of pure medicinal mineral oil, with the addition of 10 grams of non-bitter extract of cascara sagrada to each fluid ounce. It is indicated in the constipation of pregnancy constipation in nursing mothers, malnutrition attended with constipation, auto toxemia and post-operative constipation. A generous sample will be sent on request.

Physicians may satisfy themselves of the therapeutic value of this new mineral oil product by sending in the attached coupon

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Walter H Ude M D
Minn Gen Hosp Arch
Chives Phys Ther
X-Ray Rad Jan. 1931

* * * * *

"Ultraviolet irradiation produced a clinical arrest of the disease with the first treatment in 92 per cent of our cases" "(It) has none of the objectionable features of the other methods, while it seems to excel them in effectiveness. We are now using ultraviolet radiation in all of our cases of erysipelas"

W H Ude M D and
E S Platou M D, Jour
A M A. July 6 1930

"In the series of (51) cases to be described the source of ultraviolet light was a standard model air-cooled quartz lamp" "The cases treated ranged in age from 7 months to 74 years, and included 'primary' cases and cases secondary to accidental wounds, operations, and confinements. As usual there was a marked preponderance of facial cases" "The forty-seven cases treated and ending in recovery were of varying degrees of severity"

J M Davidson M D
D P H Edinburgh Brit.
Med Jour May 21 1932

* * * * *

"Good results have been obtained in this disorder with both x-rays and ultraviolet rays"

George M MacKee M D
Jour A M A. April 30
1932

* * * * *

"Clinical evidence of the value of U-V irradiation in erysipelas is amply available to all who take the trouble to study the literature on the subject before pronouncing an opinion"

R. King Brown M D
D P H Editor Brit.
Jour Actino & Physio
Sept. 1930

* * * * *

"The most remarkable results have been obtained in

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John Zahorsky M D
Am Jour Dis Child
Jan 1925

* * * * *

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(W Va Med Jour, 28 193 240, May, 1932)

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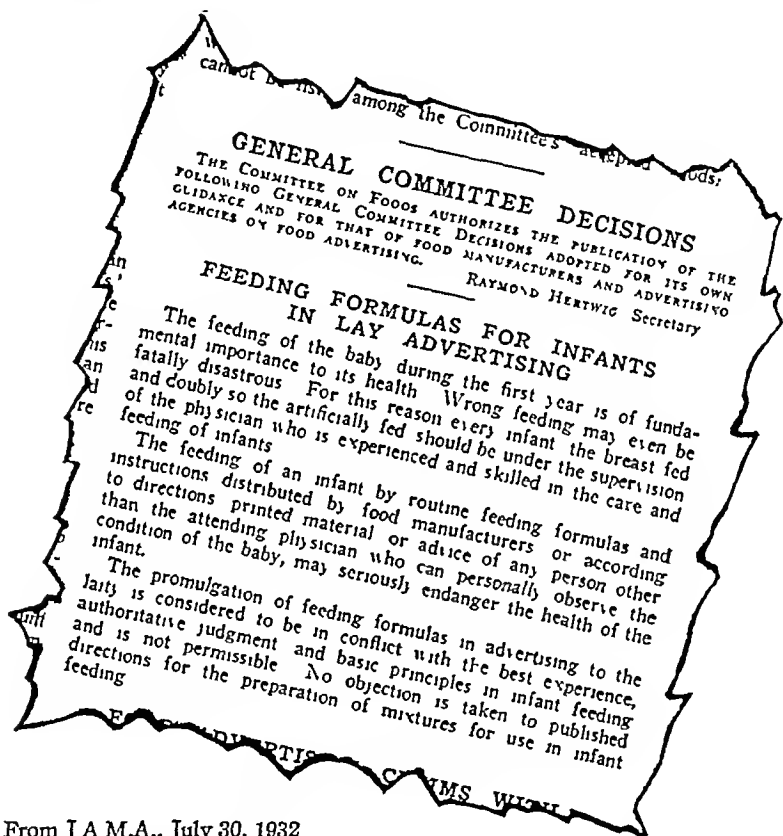
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From J A M.A., July 30, 1932

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Original Communications

PRESIDENTIAL ADDRESS AMERICAN ACADEMY OF PEDIATRICS

S McC HAMILL, M.D.
PHILADELPHIA, PA.

IN HIS admirable presidential address delivered at our meeting a year ago, Dr Morse set forth most beautifully and comprehensively the relationship that the Academy should bear to the health and welfare problems of the child and the unusual opportunities offered us as its fellows to render a high service to humanity. I would like nothing better than to repeat the substance of his address but it is not in my power to handle it with the skill and finesse that did Dr Morse.

The Academy is just emerging from the tender age of infancy and is celebrating its third birthday. Despite its youth it can point with definite pride to some real accomplishments or, perhaps one might better say, to very definite progress which augurs well for future accomplishment.

It may not be amiss therefore, to stop for a moment to consider how far we have traveled.

The Academy came into being just as the White House Conference was completing its labors. The Conference undertook the prodigious task of ascertaining what was being done throughout the country for the health and protection of the American child, what were the gaps in the program and how these gaps could be filled. The first two of these objectives were reasonably well covered but the third from lack of time was scarcely touched.

However one very vivid fact that impressed itself upon the participants in the Conference was that, if we could bring about a full and intelligent application of the knowledge we already possess, the gaps in our program for the health and protection of the American child would be considerably reduced.

Due to the clear vision of our secretary in laying the foundation for its activities the Academy has builded well to meet this important need

We have created a number of committees which, functioning properly, should have an important educational influence in the fields they represent. They should make themselves fully conversant with their subjects and make that knowledge available to the agencies working in these various fields throughout the country. Although time does not permit a detailed consideration of all the committees I would like to draw your attention to outstanding features of the work of certain committees, the need for alteration of purpose or nomenclature for others, and future opportunities for still others. The Committee on Pediatric Education has done an admirable piece of research in its field, which it is continuing and which is being made of practical value to the medical schools of the country.

The Committee on Hospitals and Dispensaries issued a most searching and valuable questionnaire to the children's hospitals of the country. Through the interest and cooperation of the Fellows of the Academy all of these questionnaires save one have been returned fully answered. It is the first time such complete information on this subject has ever been assembled. This material is being tabulated and studied. From it will evolve a picture of the children's hospital situation which will enable us to evaluate the services of these institutions and be better qualified to advise intelligently regarding them.

As Dr. Morse said in his address, "Committees are of no use unless they do something."

Some of our committees have a rather limited field of action and it might be worth while for the Executive Board to consider whether some of them may not be advantageously eliminated. There is probably no further use for the Committee on Relations with the White House Conference. The Conference has ended and its follow-up committee has disbanded. However, under a somewhat altered title it might well serve a useful purpose. There was a vast amount of valuable information collected by the Conference. Unless someone carefully reviews the transactions of that Conference and extracts the material that has practical application, there is grave danger that it will remain buried in the tomes which embody it and never be put into action.

There would seem to be a very important service for the Committee on School Health and School Health Education. Both of the subjects included in this title are under criticism. We all know how inadequate is the health supervision of the school child the country over. We also know that this service is under severe criticism by the rank and file of the medical profession on the ground that it infringes upon the prerogatives of the physician.

There certainly should be some agency engaged in a study of this entire problem to determine its objectionable features and evolve a plan by which they can be overcome

There is a prevalent impression that education in health, as given in our school systems is unsatisfactory. To determine whether this impression is justified should be our function. We certainly should know whether instruction in the important subject of health protection is being intelligently and effectively carried out in our school systems

The Committee on Mental Hygiene would seem to have not only an important but extremely interesting function. The question of the training a medical student should receive in psychiatry to enable him to cope with the behavior problems he will meet in practice, a study of the misleading literature that is being fed to young mothers and the means of combating its disturbing effect and many other interesting points offer opportunity for this committee to do an effective work

The Executive Board might also consider whether its committees are founded on the most efficient and effective basis possible. There are two kinds of committees which usually function well. One that is headed by a chairman who has a full knowledge of and is vitally interested in, the subject the committee is created to consider. In such committees most of the work, however is done by the chairman. The other is the local committee which has opportunity to bring its membership together frequently

Committees of national organizations whose membership is widely scattered and who are without salaried executives if dealing with subjects requiring constant and continuous consideration, are rarely effective. The work of the Academy committees is continuous and their membership widely scattered. The purpose of this latter point is easily evident. The Academy naturally desires to stimulate the interest and use the knowledge and ability of all of its members—a very important consideration—but from the standpoint of getting work done I am not sure the present committee plan is wise. Is it not possible to accomplish the desired result by increasing the membership of these committees, retaining an adequate geographic distribution but at the same time selecting in the community in which the chairman resides a group of four or five members who can get together frequently and support and advise the chairman? The results of the studies of the local groups could readily be submitted to the other members for review and criticism

I believe further that it would be well for the Executive Board to consider the advisability of granting each of its committees a small stipend for occasional secretarial work and necessary postage such an allowance to be based on evidence of serious activity on the part of the committee

If such a course, or some other modification of the present plan, is followed and committees still fail to function, it would seem that the Academy should give careful consideration to the advisability of using other avenues through which to accomplish its purposes

Our admirable Journal, which has had an almost unprecedented career in the first year of its existence, constitutes an excellent medium through which to extend our educational function

May it not be possible for the Journal to lay more stress on the social aspects of medicine? The fields of sociology and preventive medicine are so interrelated and each dependent so much on the other that it has seemed to me we might advantageously use the columns of the Journal for freer discussion of these interrelated problems. Can't we also lay more stress upon the protection of health? The studies of the White House Conference showed a woeful lack of application of protective procedures. They report that a very small percentage of the children had been vaccinated against smallpox or protected against diphtheria, and still fewer had had health or dental examinations. Certainly we are the logical body to popularize these important procedures and the Journal should be a useful medium for accomplishing these results

It was stated in the first issue of the Journal that "it is the intention of the editors to make it as broad and inclusive as the field of childhood itself"

We cannot expect the editors alone to attain this much desired goal. There are certainly many members in the Academy who are interested and experienced in these fields who could and should contribute. There are also many outstanding men and women in the social workers group who are keenly interested in the medical aspects of their problems and who could be induced to contribute to the columns of the Journal.

I am wondering whether the members of the Academy have responded as fully as they might to the appeal of our editors for material for the section of the Journal reserved for "News and Notes." I know that it has been the hope of our editors that this might become a very useful and interesting column. I would like to urge upon you the importance of doing everything in your power to make the Journal what I believe it can and should be, the most interesting and helpful forum for pediatric discussion in the country.

As I have reviewed, with great interest, the activities of Region II and those of the various state committees that have organized, I have become convinced that the regional and state committees offer a most effective avenue through which to accomplish many of our aims and purposes.

There are certain very definite needs we must meet and a number of obstacles we must overcome in the field of practice. The public is demanding that active measures be taken to protect the health of chil-

dren. Dr Morse has pointed out that the public 'will see to it that they are taken' As a matter of fact they are 'seeing to it' The majority of us have been indifferent to this trend

Our preventive clinics, our health centers, our state and municipal health departments, and to a less extent our hospitals, all of whose free services should be entirely restricted to the care of the indigent are daily opening their doors wider to those who can afford to pay

The medical profession is largely responsible for the fact that our potential poor patients are taking unfair advantage of this We have been fully conscious of the fact that for years the public has been plied with propaganda urging upon them the importance of health protection This propaganda has come from sources they respect and the public has been waiting for the physicians to offer them this protection The profession at large has not equipped itself to render this protection and those who are prepared have not had the courage to urge the value of health examinations and the importance of preventive procedures The natural result is that the public has sought these services where they can be had

We naturally object to this procedure but what are we doing about it? Aren't we merely standing on the sidelines and futilely shouting our protests? Have we developed a plan to *check* this trend?

The Academy through its state committees has an unusual opportunity to put effective plans into action The New Jersey committee has adopted a procedure which promises to be most effective After careful consideration Pennsylvania decided to copy this plan with certain modifications For illustrative purposes I shall refer to this Pennsylvania plan in some detail.

It calls for a state committee with county units to be under the auspices of the state medical society The officers and trustees of the Medical Society of the State of Pennsylvania were overtured by the Pennsylvania Academy Committee with the request that they accept the responsibility of creating such committees in Pennsylvania

About this time the Governor of Pennsylvania called a conference in Harrisburg to consider the best means of combating the rapidly increasing malnutrition among children that was being reported to the Emergency Relief Board which at that time was feeding 450,000 families including almost a million children

At this conference a member of the Academy Committee, having in mind the proposal put before the state medical society suggested that a state-wide Emergency Child Health Committee with county units be organized at once This proposal was adopted and the stage was immediately set for carrying out the program that had been submitted to the officers and trustees of the state society

A Planning Committee was organized, having in its membership the president, president-elect and secretary of the state medical society

If such a course, or some other modification of the present plan, is followed and committees still fail to function, it would seem that the Academy should give careful consideration to the advisability of using other avenues through which to accomplish its purposes

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As I have reviewed, with great interest, the activities of Region II and those of the various state committees that have organized, I have become convinced that the regional and state committees offer a most effective avenue through which to accomplish many of our aims and purposes

There are certain very definite needs we must meet and a number of obstacles we must overcome in the field of practice The public is demanding that active measures be taken to protect the health of chil-

strict their services to the definitely indigent groups. This calls for a new attitude of mind not only on the part of the agencies but also on the part of physicians. The latter must be prepared to render the services in health protection to those who, they believe, should be refused this service by the clinics. This will probably entail an adjustment of fees to meet the economic circumstances of this group. One of the first important points to establish is the economic basis on which free treatment should be refused. This is a wholly unsettled point but one which these county committees, with their varied representation, should be able to determine. They can also develop a plan satisfactory to the medical profession for the economic rating of those who are refused free treatment so that they may be referred to their physicians with a definite recommendation as to the fee to be charged. Such a system is in action in the Philadelphia schools in respect to eye patients and is working very satisfactorily. It was put through under the auspices of the Philadelphia County Medical Society. The reactions we have had from physicians in several of the counties of Pennsylvania have convinced us that such a plan is feasible and would be acceptable.

As has just been said, the physician must be equipped to make the necessary health examinations and to apply the essential protective procedures. We dare not put ourselves in the position of objecting to the giving of a service by others which we ourselves are not prepared to render.

This point has been taken into consideration in the development of our work in Pennsylvania. Realizing that a health examination must be the basis on which to determine the health and nutritional status of the children we are called upon to protect, the Pediatric Advisory Committee has prepared a health examination form which is officially endorsed by the state medical society. It is so formulated as to require consideration of the entire child. We feel that the making of these examinations by many physicians will have a very definite educational value. To supplement this educational feature we have prepared an explanatory leaflet which is given to each examining physician. In addition we are sending pediatricians to the County Societies that request it to discuss with them the subject of health examinations.

The State Committee of the Academy is at present engaged in formulating a plan for definite courses in preventive pediatrics to be put into operation in the autumn.

We hope through these various avenues not only to equip the physician for this service but also to stimulate his active interest.

There have been two developments in the course of the emergency work in Pennsylvania that are especially gratifying. One is the eagerness with which lay organizations and individuals have accepted medical leadership, and the other is the extraordinary cooperation we have

received from the medical profession. Of course we have had individual objectors, but up to the present time every county medical society, save one or two, that has been approached, and this includes more than three-fourths of them, has accepted the program and almost always with enthusiasm.

The officers and trustees of the state medical society are so imbued with the value of the present organization that they plan to continue it in a somewhat modified form after the present crisis is over.

While this work has been organized to meet an emergency, the procedure that was followed in its formation would have been successful even had the emergency not existed, just as has been that of the New Jersey plan. The officers and trustees of the Medical Society of the State of Pennsylvania were in process of endorsing the original proposal of the State Academy Committee when the call for the emergency committee came to them.

The emergency merely made it easier of accomplishment and earlier of realization. In other words, the emergency created the psychological moment for the development of the work. That emergencies do play a very definite part in the development of new lines of procedure in public health is evidenced by the fact that the first state health department ever created was the result of a serious emergency.

I have described the Pennsylvania procedure in some detail because I believe it creates a feasible and practicable plan to offset or cure many of the evils that have been referred to above, as well as to provide a very much needed procedure in health protection.

The State Academy Committee is not numerically strong enough in any state to make its direct efforts felt in a statewide program. On the other hand, much can be accomplished if the state committees will serve as initiating groups in interesting the state and county medical societies and the various health agencies in a manner similar to that which has been followed in New Jersey and Pennsylvania.

Through such procedure we have opportunity to make the Academy a potent force in the field of child health throughout the nation. From the date of its foundation I have been deeply impressed by the possibilities of the Academy in the relatively undeveloped field of preventive pediatrics. The measure of success we will attain depends entirely upon the seriousness and enthusiasm with which the Fellows of the Academy enter the service. It is in our power to lead the way. Let us not falter!

THE DEVELOPMENTAL HEALTH EXAMINATION

T WINGATE TODD, F R C S (ENG)
CLEVELAND, OHIO

THE NATURE OF A DEVELOPMENTAL HEALTH EXAMINATION

IN PREPARING and interweaving accounts of the developmental growth of children for the White House Conference it was a comparatively easy task to differentiate deviations from satisfactory progress so gross that they fall under the caption of ill health for it is within the training and experience of every physician to recognize frankly pathological states which require the application of restorative medicine. It was however quite another, and indeed a far more difficult problem to determine standards of optimum developmental growth. One clearly could not take the maximum as a criterion for there are aberrancies of excess as well as of deficiency. Progress, moreover, must be balanced. Physical growth may not outstep physical maturation. Nor must the physical aspect of developmental growth fall out of line with mental expansion. Mental expansion must be aligned with emotional stability. Experience has great influence in the transformation of capacity into ability. Interests play their part. Talent that most unpredictable of all human traits, cuts right across the path of progress and brings its own influence to bear on the developing personality. In attempting to outline healthy developmental progress we have then to consider quite other features than those which determine medical health.

Medical health is essentially a record of status. developmental health is essentially a record of progress. That is why the serial examination is necessary for the latter determination.

Developmental health presupposes absence of any gross deviations from medical health. Hence the developmental health examination may include but does not necessarily imply a medical health examination. In my report on the assessment of physical status¹ to the White House Conference it was necessary to build such program of developmental health as we then had upon the routine medical examination. Since that date, the Developmental Health Inquiry of the Associated Foundations in Cleveland has provided the opportunity of outlining in more definite terms those assessments which give us information upon developmental progress. In the Cleveland experimental study these are subdivided into physical, orthodontic, psychological and sociological groupings. Under the physical heading come measures of growth, of maturation, of posture and of nutritional progress. The

¹From the Laboratory of Anatomy Western Reserve University and Associated Foundations.

orthodontic group includes assessments of facial growth, of dental calcification and eruption and of the proper development of nose and nasopharynx. In the psychological group are estimates of muscular power and coordination, of personal social reactions, of reasoning and the handling of factual material, of mechanical intelligence and ability, of self-reliance and emotional stability. The sociological determinations are those of socio-economic stability and advantages, of family integration and group acceptance.

Although we are still in the exploratory phase of the subject and many of these measurements are not yet simplified so that they can be effectually and economically put into practice on a large scale, the day is not distant when an adequate developmental health assessment will be devised of so simplified a character that it can be applied in the course of regular practice. And some of the tests at least may even now be utilized with distinct advantage by the pediatrician.

THE CONDUCT OF A DEVELOPMENTAL HEALTH EXAMINATION

A. Physical Growth—The significant measurements of physical growth are weight, recumbent length, stature, height of left iliac crest from floor, greatest breadth over iliac crests, bitrochanteric diameter, and length of tibia from articular edge of inner tuberosity to tip of tibial malleolus. Chest measurements and expansion, it must be observed, like vital capacity, fall under the medical examination. The difference between stature and recumbent length gives a measure of posture. The height of iliac crest gives the proportion of leg length to stature. Bi-iliac and bitrochanteric diameters are really measures of maturation. Tibial length is the most easily obtained measure of growth in a limb bone for comparison with stature.

B. Physical Maturation—For the estimation of physical maturation roentgenograms are necessary. Between birth and fifteen years these should comprise anteroposterior of left hand and wrist, dorsoventral and lateral of left foot and ankle, posteroanterior of left knee. All four can with care be taken on two 8 by 10 inch films. Between twelve and fifteen years an anteroposterior roentgenogram of the elbow is of assistance but not really necessary. Between fifteen and twenty years elbow and foot are not required. At that period of adolescence the hand and knee roentgenograms should be taken on a single film and a second film used for shoulder. The details of technique and interpretation are given in my account of roentgenographic appraisalment for the White House Conference.⁹

C. Orthodontic Appraisalment—This is a somewhat specialized assessment the details of which have been fully set forth by my colleague, Dr. B. H. Broadbent,² and its application to the study of nasal passages and adenoid growth will shortly be published by Dr. H. C. Rosenberger.⁵

D Psychological Assessment—The psychological progress is ascertained by tests appropriate to the age and type of mental expansion on which information is desired. For children of eighteen months or less the Gesell tests are of service. From two to six years the Merrill Palmer tests give a measure of intelligence expressed in performance. Motor tests are employed to give a measure of muscular coordination. The Binet test of course measures intelligence expressed vocally, though it assesses only pure reasoning and the handling of factual material. Other tests of useful character are the man drawing test, the Minnesota mechanical abilities tests and paper form board, the Ascendancy-Submission test, the Woodworth Mathews personality rating and the Bernreuter Inventory.

E Sociological Appraisalment—The sociologic investigation is still less ready for general application though the Sims socio-economic rating scale gives some measure at least of socio-economic advantages.

THE APPLICATION OF ROUTINE DEVELOPMENTAL HEALTH DETERMINATION TO PEDIATRIC PRACTICE

Accepting the fact that so far, the sociological and orthodontic tests are insufficiently simplified for general use and that psychological assessment demands special training and is therefore as yet very restricted in its applicability to routine practice we still have the measures of physical appraisal which can be utilized at once and interpreted with fair assurance after a little experience. The technique is simple, the cost low and the interpretation not too difficult to be mastered by the busy practitioner.

I THE SIGNIFICANCE OF PHYSICAL MEASUREMENTS

The physical measurements selected above will determine the tempo of actual increment in size. They should be compared with the White House Conference tables or those prepared by R. M. Woodbury for children under six years¹² and for older white children by Baldwin and Wood¹ or for colored children by Royster and Hulvey.¹⁴ It is true that the Woodbury standards are rather low but we find in practice so many children whose status in physical growth is mediocre though their progress between examinations is satisfactory that the Woodbury standards are really of great practical advantage for they rarely compel the physician to explain to a parent why the child's progress is not at least average in amount. There are, however, far more important deductions to be drawn from growth progress than the simple satisfaction of parental ambition. In a way increments of weight if paralleled by proportionate increments in stature during the infancy and preschool phases, are measures also of physical maturation. At least the two phases of developmental growth are very closely correlated. And the mental development, in the majority of

healthy children, keeps pace with the physical growth. It is our experience that the child who has, by his third birthday, reached the stature and weight of an average five-year-old child as designated on the Woodbury tables, will also have reached approximately the five-year stage in physical maturation and mental progress. It is important to realize that whereas the body takes some eighteen to twenty years to reach adult growth, the brain has practically reached adult size by the sixth birthday. The changes in cerebrum attained after that date seem to be connected with the development of association centers and connections which reduce the depth of the fissural pattern.³

The psychologists tell us that the type of mental development changes fundamentally after the age of six years so that, instead of being an elaboration of capacity, it takes the form of a training in ability.⁴

Children who grow and mature rapidly before the age of five years must not be expected to continue at this tempo during the grade school period. There is, as it were, a plateau of progress which may be attained early or late. Those who reach it early diminish their rate of progress so that by five years there is a greater uniformity of size and maturation than at any earlier period excepting perhaps the first birthday.

After the stage reached between five and six years one may expect, during the grade school period, another phase of increased growth velocity lasting a year or two and expressed in children of good physical constitution rather earlier than in those of less satisfactory developmental health but showing itself in all children under the age of nine years. It is followed by diminished activity of growth during the period of approximately nine to eleven years. After this renewed vigor of growth sets in with the approach of adolescence.

Allergic children begin to change their type of growth progress about the age of seven years. Their stature increases out of proportion to their weight and the lean "bean-stalk" type of child begins to show itself. Kretschmer's types indeed are obvious during adolescence but their body form is already demonstrable at a much earlier age.

The early adolescent growth in stature, when expressed on the Baldwin-Wood or Royster-Hulvey standards, is more vigorous in boys than in girls but this is largely a matter of comparison with adult stature. The girl reaches her full height at an earlier age than the boy and therefore the increase in pelvic dimensions is more obtrusive in the girl at this stage. The increase in bitrochanteric diameter is partly due to accumulation of panniculus but is also produced by growth of femoral neck and lateral displacement of great tuberosities of the femora. It occurs rather earlier than the increase in bi-iliac diameter which, in its turn in girls, precedes and accompanies the establishment of the menstrual periods.

Relatively late occurrence of the menarche seems to imply delay in the cessation of stature increase and in union of the epiphyses, girls of this type grow taller than those whose menarche supervenes early, largely because growth is possible in them over a longer period of the second decade

Stature increase in boys remains possible through a greater part of the second decade and their adult height is much greater on the average than that of girls, a sex difference which is distinctly anthropoid in character since it is far more characteristic of higher primates than of lower primates or non primate mammals

In all interpretations of stature and weight increase the family hue characteristics must be reckoned with but nutrition and medical health play a significant rôle as is well seen in Mitchell's studies of Porto Rican children compared with those of the continental United States In general stature and weight increments beyond the average are a rough measure of constitutional health but, also generally speaking they are of less significance in this respect than the roentgenographic appraisalment of physical maturation

II ROENTGENOGRAPHIC APPRAISMENTS

The roentgenograms suggested earlier in this survey shed a very significant light on developmental growth and health if carefully studied and properly interpreted They give measures of mineral reserves and therefore of constitutional fitness, of constitutional vulnerability, and of physical maturation These three features should be considered separately

The Estimation of Mineral Reserves—Without going into detail on the subject of mineral reserves it may be recalled that Sherman has emphasized the iron rich calcium poor status of the infant⁷ This, however, has no necessary relation to blood calcium studies since blood calcium is merely calcium in transit without indication of its source or destination Its significance for bone growth neuromuscular progress and kidney function are, however evident enough The chief depots of mobile calcium are the metaphyses of the long bones of the limbs and the bones of the hands and feet Demineralization from whatever cause, as in the osteoarthritic period in pregnancy in adolescence or in infancy makes its appearance chiefly in these areas In the dimineralization of rickets, epiphyses or carpal bones already ossified may lose their calcium so that they appear as 'ghost centers' in the roentgenogram We are not concerned in developmental health, with extreme conditions such as this but with the fluctuations observable in the mineralization of the skeletal depots Epiphyseal ossification in infancy and early childhood is but one phase of this mineralization study Breast fed babies show a slower progress of epiphyseal ossification whether or not cod liver oil is administered, than babies

fed upon a non-maternal diet During the period of adjustment to non-maternal diet the progress in epiphysial ossification is quite slow but a rapid increase in progress is a measure of the completion of adjustment Babies on cow's milk with cod liver oil show more vigorous progress in the epiphysial ossification schedule between six and twelve months than babies upon other formulae Boys tend to a slower progress than girls in epiphysial ossification in the latter half of the first year but make up for this tardy progress once they have passed the first birthday These distinctions still require much further investigation but they are quite evident in a carefully controlled study Accompanying them can be seen fluctuations in the mineralization of cancellous texture and of compacta though no adequate measures of quantitative determination have yet been devised The fluctuations are so great that quantitative methods are not necessary for their recognition

DeminerIALIZED infants maintain their functional progress as determined by tests of the Gesell type on motor responses, motor adaptability, and on personal social responses, and even in physical growth for some weeks, though, in a while, they fall behind in the motor and adaptive responses, and, somewhat later, in personal social responses There is a distinct change in behavior they become restless, irritable, apprehensive, and querulous Once these behavior changes have appeared the replenishing of the skeletal depots will not be accompanied at once by a return of serenity in behavior, though the motor responses recover very quickly and often will promptly improve on the administration of an adequate dose of cod liver oil

The deminerIALIZED infant is not necessarily sick though disturbances of an exudative or allergic type readily supervene When that happens the child has passed from the fluctuation of developmental health to the decompensation and failure of reserves culminating in medical ill-health

The vitamin ration, especially of A, B, and G seems to be closely associated with mineralization and the maintenance of constitutional health in infancy I do not emphasize vitamins C and D, adequate doses of which are usually provided

The rôle of demineralization as expressed in roentgenograms and affecting developmental growth in childhood cannot be touched upon in this survey which is designed merely to open the subject

The Recognition of Constitutional Vulnerability—The determination of damage suffered in constitutional health as the result of an infectious disease or other disturbance of medical health is often a matter of considerable import The parental measure of a child's actual illness is frequently determined by the resultant disturbance of household routine But in the absence of evident sequelae we have no adequate measure of the real constitutional setback The lines of in-

interrupted growth evident on roentgenograms, especially between the third and fourteenth year, emphasized by Park, of Hopkins, give not only an estimate of the severity of the impact upon developmental growth but also of its date. This can be determined easily within a month of the occurrence if the bodily growth increments are known from serial developmental health examinations. Further, the length of time which the transverse line or "scar" remains is an indication of severity, for the longer it takes the bone to remodel its architectural pattern to eliminate the mark the greater the constitutional disturbance. There is some selective activity in these markings on the bones for the lower tibia seems to bear the brunt of dietetic disorders especially those of minor grade, whereas the lower radius, lower femur, and upper tibia are more often scored by the effects of the exanthemata. Much more could be said on this subject if space permitted even though the full story is by no means yet understood.

The Assessment of Physical Maturation—It has previously been mentioned that below the age of five years physical measurements give a fair indication of the progress of development or as the theme is better expressed, of progress in maturation. During the grade and high school periods however, physical measurements express growth only, as increase in dimensions. They do not, except in pelvic dimensions possess any relation to bodily maturation. To determine progress in this aspect of developmental growth roentgenograms are necessary. During the grade school period extension of ossification into the cartilaginous epiphyses and, during the high school age epiphysal union permit determination of the stage attained in progress toward maturity of the skeleton. Empirically this progress is found to be closely related to general bodily maturation. The details of roentgenographic appraisal have been outlined in the White House Conference reports.⁹⁻¹⁰ Measurement of carpal areas resorted to by many workers is an effort in this direction but unsatisfactory in practice, since no adequate standards of measurement are possible in that portion of the skeleton which is one of the most susceptible to disturbance as a result of ill health or nutritional deficiency. Standards of progress in maturation, other than those in the White House Conference reports, suffer from lack of precision since they presuppose a range of individual variation. Individual variation does indeed occur when the maturation stage is matched against chronological age but obviously no precise determination can be made upon a scale involving range any more than upon any other scale the gradations on which are blurred and indefinite. Actual practice in rating of roentgenograms in terms of the details of penetration or of epiphysal union alone can give confidence in this new and exact instrument for measuring physical maturation.

MEASURES OF SUPERIORITY

It is a simple matter to define a child as tall or heavy for his age, a child who looks old for his years, or a child with a high I Q. But it is the discovery that physical maturation can be exactly determined which has rendered possible the intimate correlation of physical growth and mental expansion. A child may be tall and slender and high in Binet rating as most allergic children over seven years actually are, but until the physical maturation progress has been measured we have no adequate conception of the child's actual status. A child may be tall or short for his age but the stage reached in his physical maturation is the really significant factor in determining the more subtle personality traits which interplay with the mental expansion. A superior type of child, that is a child who has had the advantages of good nurture, adequate socio-economic advantages, and reasonable freedom from disturbances of health and of developmental growth, is tall for his age, of weight a little beyond the average for his height, of physical maturation several months or even two years above the mediocre mean for his years, and of a psychologic rating easily in advance of the average for his age. Harmonious superiority implies an approximate equality of advancement in all these features. Disharmonious superiority or precocity is the result of unequal progress in which one feature far outstrips the others.

RETARDED AND PATHOLOGICAL DEVELOPMENTAL GROWTH

The distinction between retarded and pathological developmental growth is evident even when it cannot be defined. Many girls and still more boys are tardy in entering their adolescent phase but, given time, they will make good the delay the only permanent objective result of which is an increased stature, though there are definite personality modifications and traits which may become permanently impressed upon the individual. A pathological interference with adolescent progress is recognizable in character of subcutaneous tissue, in body proportions, in personality traits as well as in the fact, ascertainable at last, that time alone does not suffice to eliminate the handicap to progress. For such children treatment is necessary. This should be directed toward the reestablishment of metabolic integrity rather than specific medication for growth stimulation. A good example is given by Dr. Priscilla White's diabetic children.¹¹ These children retarded, both in physical growth and physical maturation, at once began to repair both aspects of the deficiency when they were placed on regular doses of insulin. A similar and more generally recognized type is the hypothyroid child. There are, however, many children subthyroid in diathesis, not retarded enough to merit the definition of hypothyroidism. Roentgenographic determination of physical maturation permits the recognition of many lesser degrees of retardation.

more temporary in character and usually self rectifying in time, following the exanthemata and other forms of health disturbance. In infantilism is one of the most intractable of these forms. Further consideration of this aspect of our problem would bring us back into the medical health examination from which we sought to free ourselves in elaborating the theme of the developmental health assessment.

SUMMARY

1 A medical health examination is an assessment of constitutional status; a developmental health examination is an assessment of specific progress in physical growth and maturation, in mental expansion, in emotional stability, and in other aspects of normal healthy childhood.

2 The conduct of a developmental health examination calls for certain types of measurement which are discussed in some detail in the body of this paper.

3 Some of these determinations may readily be incorporated in the routine pediatric serial examinations, especially the determinations of physical growth and maturation which properly interpreted throw a very significant light on the progress of growth in childhood.

4 Of these determinations now available the roentgenographic investigation holds the greatest immediate promise.

5 Greater precision in definition of the superior type of childhood is easily attainable as well as in the segregation of simple and self rectifying types of retardation from the pathological forms which call for medical supervision to restore metabolic integrity.

6 The developmental health examination opens up a new vista of understanding in the problems and personality of the healthy growing child.

REFERENCES

- 1 Baldwin, B. T., and Wood, T. D. *Weight Height Age Tables*. Iowa Child Welfare Research Station, Iowa City, 1927.
- 2 Broadbent, B. H. *Anglo Orthodontist* 1: 45, 1931.
- 3 Donaldson, H. H., and Addison, W. H. F. *Jour. Comp. Neurol.* (In press.)
- 4 Johnson, Buford. *Child Psychology*. Springfield and Baltimore, 1933. Charles C. Thomas.
- 5 Rosenberger, Harry C. *Upper Respiratory Development Expressed in Facial Growth*. (In preparation for press.)
- 6 Royster, L. T., and Hulvey, C. N. *Am. J. Dis. Child.* 38: 1223, 1929.
- 7 Sherman, H. C.: *Nutrition Abstracts and Reviews* 1: 617, 1932.
- 8 Todd, T. Wingate. *White House Conference Reports, Growth and Development of the Child, Part IV, Appraisal of the Child*. New York, 1932. Century Co., pp. 286-330.
- 9 Todd, T. Wingate. *White House Conference Reports, Growth and Development of the Child, Part IV, Appraisal of the Child*. New York, 1932. Century Co., pp. 258-279.
- 10 Todd, T. Wingate. *White House Conference Reports, Growth and Development of the Child, Part II, Anatomy and Physiology*. New York, 1933. Century Co., pp. 65-78.
- 11 White, Priscilla. *White House Conference Reports, Growth and Development of the Child, Part I, General Considerations—Diabetes*. New York, 1933. Century Co., pp. 351-356.
- 12 Woodbury, R. M. *1921. Statures and Weights of Children Under Six Years of Age*. Washington, 1921.

THE MEASUREMENT OF ABERRANT DEVELOPMENTAL GROWTH

I THE MANAGEMENT OF PREADOLESCENT DISTURBANCE

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THE SUBTHYROID STATE

ANOMALIES of human stature, proportionate growth and maturity level, more especially gigantism and dwarfism, have always fascinated the investigator. Quite recently, with the accumulating knowledge of ductless glandular physiology, disturbed metabolic states have been carefully studied and numerous theories have been advanced to explain the effects of altered metabolism on the progress and end-result of growth and development.

Recent experience emphasizes the value of skeletal assessment in the diagnosis and treatment of disorders which involve growth in size or progress toward the mature condition. In our laboratory more than two thousand complete human skeletons and more than thirty-six hundred living individuals below the age of twenty-five, studied roentgraphically, have been used to elaborate standards of progress in maturation. Todd^{1 2 3 4} and Stevenson⁵ have reported this work. These standards have been utilized in the assessments to follow since they have been worked out and tested more fully than other devices of similar nature. It is possible by this method to estimate the stage of ossific development within a six-month range.

In the study and treatment of aberrant growth it is important to evaluate the anomalous progress toward maturity in the individual. Indeed it is in this aspect of developmental growth that the first evidence of a disturbed metabolism is to be found. Engelbach and McMahon⁶ and Shelton⁷ have recently emphasized the retarding effect of hypothyroidism. The current tendency, however, to speak of maturation solely in terms of sexual maturity does not adequately interpret the maturation process. Differentiation of features indicates, as clearly as growth in stature, a constant structural change just as significant in its assessment before adolescence as at that precise phase of life. The W R U standards evaluate these structural changes throughout childhood and adolescence and are proving valuable in the understanding of all types of failure in the attainment of average developmental progress. In the first volume of the White

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Honse Conference reports on Growth and Development⁶ some of the conditions which lead to a severe lag in maturation are discussed. Diabetes, for example as well as hypothyroidism and other altered metabolic conditions handicaps the growing child in that it retards his progress toward maturity as well as the attainment of his average family stature.

INDIRECT DEVELOPMENTAL GROWTH PROMOTION

In these special cases we have studied both retardation in growth and retardation in development using, for this purpose anthropometric, clinical, developmental, and psychometric techniques and bringing each

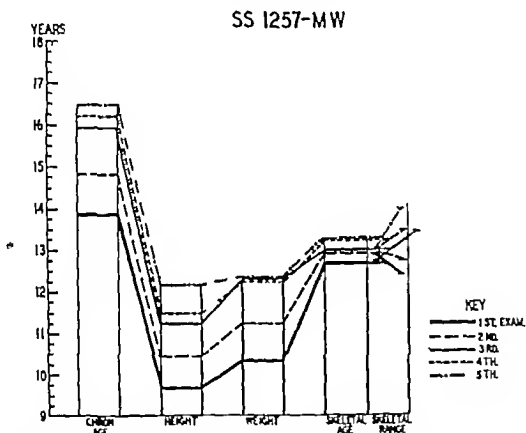


Fig. 1—Chart of growth and maturation progress of SS 1257 male, white, from the age of thirteen years ten months to sixteen years five months. Treatment only after third examination at fifteen years eleven months. In skeletal range downwardly directed lines signify retardation upwardly directed lines, progressive maturation.

patient into the laboratory at three month intervals for study while under active treatment. Nearly 200 cases of disturbed development have been recorded and more than 35 cases are being studied and treated at the present time. We have observed that when a nutritional disorder occurs in a growing child, there is a disturbance of developmental growth. In the majority of children this interruption is temporary and the normal progress is again resumed during the period of convalescence. In a few children, following such a disturbance there is no resumption of the original tempo of progress, as though the mechanisms which control growth and development had been definitely mutilated. In these cases a progressive developmental lag be-

comes apparent and adult proportions or complete maturity may never be reached. A dwarfism or at best a defective maturation results.

In the treatment of these conditions the administration of certain endocrine substances appears to rectify the metabolic functions of the organism and thus promote developmental growth. It is, however, essential to govern the dose by a serial study of developmental growth progress during the treatment. The following cases illustrate how progress under therapy is studied and indicate the promotion of growth at a rate greater than that shown in normal children under our observation or in cases of aberrant growth not under treatment.

SS 1257 shows a lag both in stature increment and in maturation, with the progress in stature following growth promotion (Fig 1

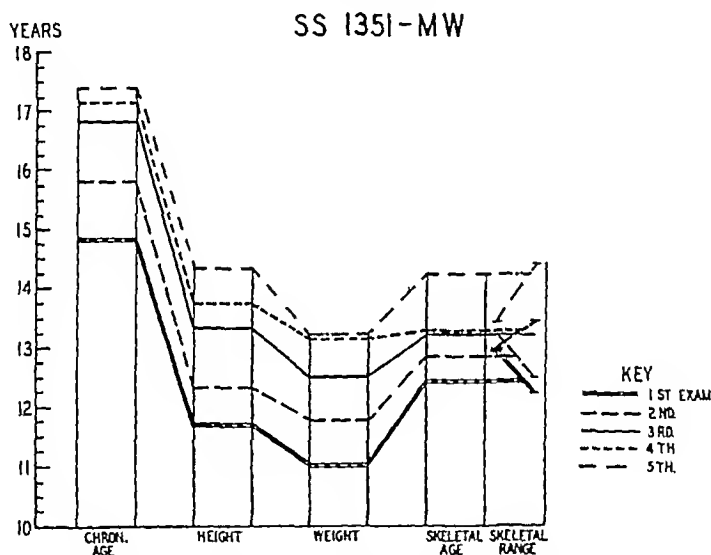


Fig 2—Chart of growth and maturation progress of SS 1351 male, white from the age of fourteen years ten months to seventeen years four months. Treatment only after fourth examination at seventeen years one month. In skeletal range downwardly directed lines signify retardation upwardly directed lines progressive maturation.

Table I) During the first two years while the boy was being studied but not treated, height, weight, and maturation showed much less than the average yearly increments, so that on his sixteenth birthday the boy was retarded the equivalent of four years eight months in height, three years seven months in weight on the Baldwin-Wood standards, and two years nine months in maturation on W R U standards. During the next six months Armour's desiccated thyroid (4 grains) and Armour's desiccated anterior pituitary (2 grains) were administered daily by mouth. Assessments then registered a height increase equivalent to eleven months on the Baldwin-Wood standards, a stationary weight, and a maturation (or developmental) increment

TABLE I
pg 1257

SEX	AGE	HEIGHT		WEIGHT		SKEL. AGE		SKEL. RANGE (TODD)
		(IN.)	(BALDWIN WOOD)	(POUNDS)	(BALDWIN WOOD)	(TODD)	(TODD)	
1	13 yr 10 mo.	1353	9 yr 8 mo.	74½	10 yr 4 mo.	12 yr 8 mo.	12 yr	5 mo to 1-yr
2	14 yr 0 mo.	1380	10 yr 5 mo.	70	11 yr 3 mo.	12 yr 11 mo.	12 yr	9 mo to 13 yr
3	16 yr 11 mo.	1433	11 yr 3 mo.	87½	12 yr 4 mo.	13 yr 0 mo.	1-yr	0 mo to 13 yr
4	16 yr 2 mo.	1416	11 yr 6 mo.	86	12 yr 3 mo.	13 yr 3 mo.	13 yr	0 mo to 13 yr
5	16 yr 6 mo.	1470	12 yr 2 mo.	86½	12 yr 4 mo.	13 yr 3 mo.	13 yr	0 mo to 14 yr

During two years without treatment the increases are:

Height equivalent	19 mo
Weight equivalent	24 mo
Skel. age	4 mo.

After six months' treatment the increases are:

Height equivalent	11 mo
Weight equivalent	0 mo
Skel. age	3 mo

Table 11
SS 13,1

SEX AND AGE	CHRON. AGE	HEIGHT (MM.)	HEIGHT- EQUIVALENT		WEIGHT (POUNDS)	WEIGHT- EQUIVALENT		SKEL. AGE (TODD)	SKPL. RANGE (TODD)
			(BALDWIN WOOD)	(BALDWIN WOOD)		(BALDWIN WOOD)	(BALDWIN WOOD)		
1	14 yr 10 mo 0 days	1447	11 yr	8 mo.	77½	11 yr	0 mo.	12 yr	3 mo to 12 yr
2	15 yr 9 mo 20 days	1484	12 yr	3 mo	82½	11 yr	0 mo	12 yr	0 mo to 13 yr
3	16 yr 10 mo. 2 days	1537	13 yr	4 mo	88½	12 yr	0 mo.	12 yr	11 mo to 13 yr
4	17 yr 1 mo 24 days	1670	13 yr	9 mo	96½	13 yr	2 mo	13 yr	0 mo to 13 yr
5	17 yr 4 mo 31 days	1600	14 yr	4 mo	96½	13 yr	3 mo	13 yr	6 mo to 14 yr

During two years without treatment the increases are:

Height equivalent	18 mo	Height the increases are
Weight equivalent	18 mo.	Height equivalent
Skel. age	0 mo.	Weight equivalent
		Skel. age

12 mo	12 mo
9 mo	9 mo
12 mo	12 mo

equivalent to three months on the W R U standards This case is recorded merely as an example of the encouragement of stature increase in retarded adolescence

SS 1351 is a similar case in which the developmental progress was materially modified following treatment (Fig 2, Table II)

After two years of simple observation, when this boy was sixteen years ten months of age he was still retarded the equivalent of three years six months in height, four years four months in weight on the Baldwin-Wood standards, and three years seven months in development on the W R U standards Further, the retardation was progressive during the two preceding years when no treatment was given In

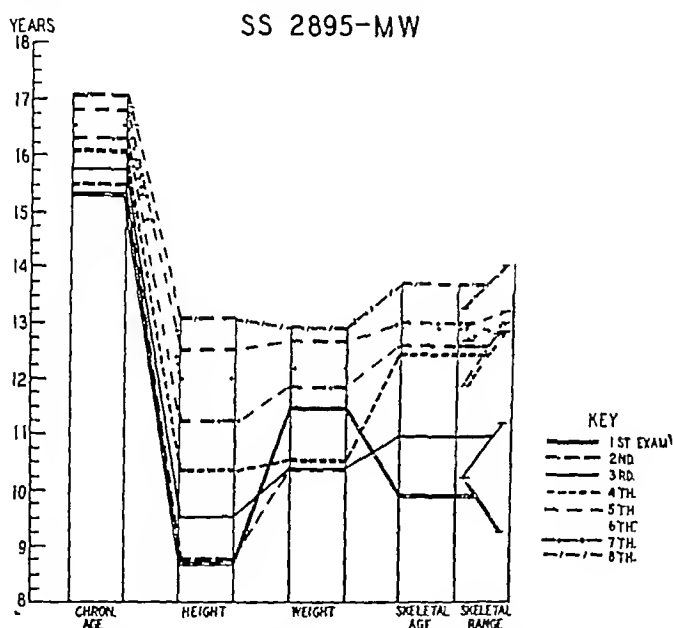


Fig 3—Chart of growth and maturation progress of SS 2895 male white, from the age of fifteen years four months to seventeen years. Treatment throughout entire eight examinations. In skeletal range downwardly directed lines signify retardation upwardly directed lines progressive maturation.

the six months following the institution of treatment the patient grew the equivalent of twelve months in height and nine months in weight. He also progressed the equivalent of twelve months in development. During this time he received 2 grams of desiccated thyroid and 2 grams of desiccated anterior pituitary for three months, then 4 grams of each for three months. This is again an illustration of developmental growth encouragement in retarded adolescence.

The detailed relationship of endocrine dosage to progress in developmental growth is presented in the following case (SS 2895), the features of which clearly indicate that a therapeutic program for the promotion of specific effect either of increase in dimensions or of pro-

TABLE III

SS 2395

EXAM	CHRON. AGE	HEIGHT (MM)	HEIGHT EQUIVALENT (BALDWIN WOOD)	WEIGHT (POUNDS)	WEIGHT- EQUIVALENT (BALDWIN WOOD)	SKEL. AGE (TODD)	SKEL. RANGE (TODD)
1.	13 yr 4 mo 13 days	1810	8 yr 8 mo	84½	11 yr 6 mo	9 yr 11 mo.	9 yr 3 mo to 10 yr 3 mo
2	15 yr 6 mo 6 days	1312	8 yr 8 mo	74½	10 yr 4 mo.	(No roentgenograms made)	
3	15 yr 0 mo 7 days	1347	9 yr 0 mo	74½	10 yr 4 mo	10 yr 11 mo	10 yr 3 mo. to 11 yr 3 mo
4	16 yr 0 mo 13 days	1387	10 yr 4 mo	15½	10 yr 0 mo	12 yr 5 mo	11 yr 9 mo to 12 yr 11 mo
5	16 yr 3 mo 06 days	1446	11 yr 2 mo	93	11 yr 10 mo	12 yr 7 mo	11 yr 0 mo to 12 yr 11 mo
6	16 yr 6 mo 00 days	1460	12 yr 0 mo	80½	12 yr 8 mo	12 yr 11 mo	12 yr 9 mo to 13 yr 0 mo
7	16 yr 9 mo 19 days	1492	12 yr 6 mo	90	12 yr 8 mo	13 yr 0 mo	12 yr 11 mo to 13 yr 3 mo
8	17 yr 0 mo 18 days	1502	13 yr 1 mo	92½	12 yr 11 mo	13 yr 0 mo	13 yr 3 mo to 14 yr 0 mo.
After twenty months' treatment the increases are							
		Height	212 mm (8½ in.)	Height equivalent		4 yr 5 mo	
		Weight	675 lb	Weight equivalent		1 yr 5 mo.	
		Skel. age	3 yr 10 mo				

gressive maturation can indeed be worked out. This case particularly illustrates the adjustment of endocrine dosage for the promotion of growth and emphasizes the significance of a serial maturation study (Fig 3, Table III)

SS 2895 was first studied in this laboratory on May 9, 1931. The boy had been a feeding problem during the first two years of his life, after which time he failed to grow normally. At the age of four he had measles, at five chickenpox and at six

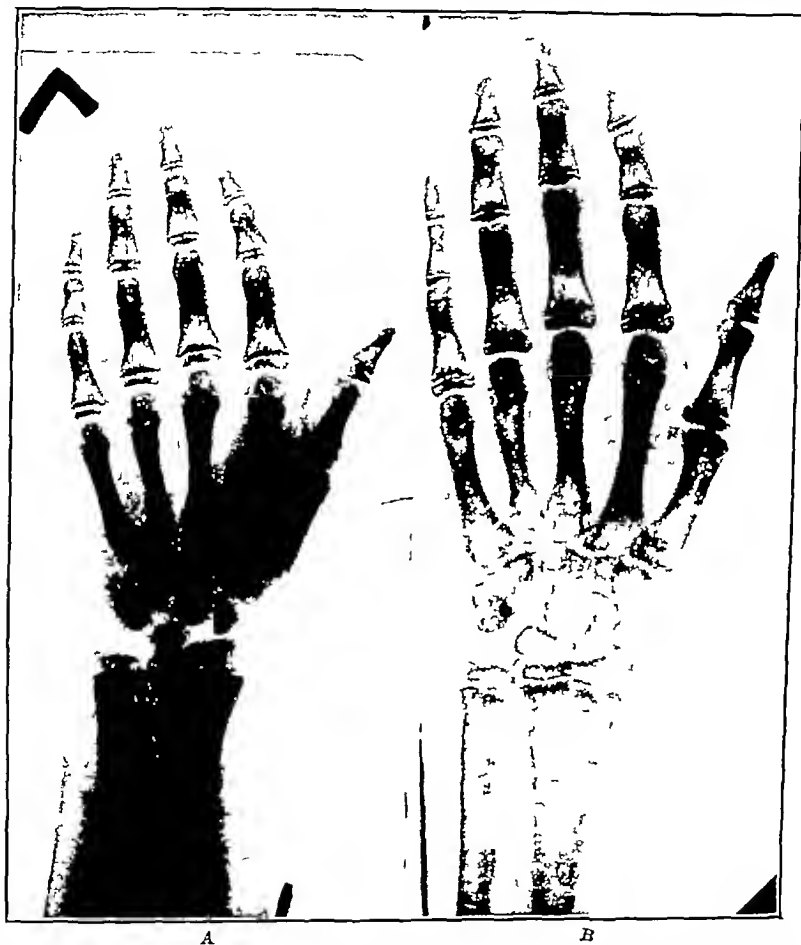


Fig 4—A Roentgenogram of left hand SS 2895 before treatment aged fifteen years four months. B Roentgenogram of left hand SS 2895 after twenty months treatment, aged seventeen years.

mumps. Other than this his history was uneventful. His parents are both above the average stature and his family history is negative.

In 1926 he had a course of both thyroid and anterior pituitary substance by mouth and became so nervous that after two months treatment was discontinued. In 1928 he had another course of thyroid treatment but this was also discontinued because of nervousness and irritability.

When first examined in our laboratory he was a fairly well proportioned boy, somewhat lethargic, fifteen years four months thirteen days of age. His voice

had not changed. There was no axillary, pubic, or facial hair. The skin and hair were very dry and the subcutaneous tissues were unusually firm. The genitalia were underdeveloped; testicles about one and one half centimeters in diameter and penis four centimeters in length. There was also an underdevelopment of the maxillary part of the face with an associated constriction of the posterior nasal passages. The basal metabolic rate registered minus 10 per cent and minus 17 per cent on two estimations. Other laboratory chemical tests revealed nothing unusual.

The physical assessment at this time (Exam. 1, Table III) gave the boy a height age of eight years eight months, weight age of eleven years six months on the Baldwin Wood standards, and a skeletal age of nine years eleven months on our



Fig. 5.—A Roentgenogram of left knee before treatment SS 2395 fifteen years four months. B Roentgenogram of left knee after treatment SS 2395 seventeen years. Note transformation of cauliflower-like mineralization of patella into normal ossification after twenty months.

standards. There was a marked osteochondritis of the patella and of the navicular bone of the foot.

At this time Armour's thyroid gland tablets were prescribed 2 grains each day and Armour's anterior lobe pituitary tablets, 4 grains a day. Two weeks later the dose was increased to thyroid 4 grains, and pituitary, 6 grains. This dosage produced headache, sleeplessness and a mild glycosuria. It was therefore reduced to 2 grains of thyroid and 6 grains of pituitary a day. Two weeks later the glycosuria and other disturbances had disappeared and the 4 grain thyroid, 6-grain pituitary dosage was resumed. No further disturbances occurred.

After two months of this régime (Exam. 2, Table III) the boy had lost ten pounds in weight and had not increased in height. The skin was then not so dry and the subcutaneous tissues had lost their unhealthy firmness.

A SURVEY OF ONE HUNDRED CASES OF CONGENITAL SYPHILIS TREATED WITH STOVARSOL (ACETARSONE)

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DURING the past few years the use of stovarsol (acetarzone*) in the treatment of syphilis, especially congenital syphilis, has been detailed by a number of writers^{1,2}. A survey of 100 cases of congenital syphilis thus treated seems desirable at this time. Our treatment was patterned after that of Bratusch-Mairrain, which is as follows: 0.005 grams of the drug per kilo body weight is given for one week, followed by 0.010 grams per kilo daily for one week, 0.015 grams per kilo daily for one week, and 0.020 grams per kilo daily for six weeks. This is followed by a rest period of one month and the course repeated until the serologic tests are entirely negative, and three courses are given thereafter. A rest period of six months is then given and then one more course of treatment.

The serologic tests used by us consist of a Wassermann reaction, using acetone insoluble and cholesterinized antigens, and a Kahn test. In our series there were 46 cases in which treatment was begun in the first year, and 54 cases in which treatment was started in children over one year of age. This division is made because treatment in the young infant results, as a rule, in prompter clinical and serologic improvement.

TOXIC REACTIONS

Toxic reactions occurred three times in the older group and twice in the younger group. In this latter group there were 3 patients who developed toxic reactions in whom it was doubtful that the symptoms were due to stovarsol. Thus the percentage for the series showing toxic reactions was 5 and possibly 8. Most of these reactions were very mild, consisting of an erythema and in a few cases a rise of temperature. Diarrhea did not appear as a toxic symptom in our series of cases, when it was present it was due to some other cause. In one patient a girl of ten and a half years, there was a marked erythema when given sulpharsphenamine, but no reaction to stovarsol.

Three patients in the older group showed toxic reactions. One was a boy, three years five months old, who developed a generalized macular rash twelve days after beginning treatment. Stovarsol was dis-

From the syphilis clinic of the Childrens Memorial Hospital Chicago Ill.
*Acetarzone is the name used in New and Non official Remedies of the American Medical Association and is the same chemically as stovarsol and spirocid. The drug stovarsol used in this series was kindly furnished to us by Merck & Co.

continued for two weeks and then resumed without reaction. The second patient, a girl five years nine months old, developed an erythema on the dorsal surfaces of the upper and lower extremities a few days after treatment was begun. No treatment was given for a week. The rash disappeared and treatment with stovarsol was begun again, this time without reaction. The third patient, a white girl of seven years, had an interstitial keratitis. After three weeks of treatment she developed an erythema over the upper chest and the dorsal surfaces of the upper and lower extremities together with fever up to 102.5°F . Stovarsol was discontinued and begun in ten days when a similar cutaneous and febrile reaction occurred. Stovarsol was not attempted again. During this time, however, the keratitis made very rapid improvement the right eye almost clearing, and the left cornea remaining only slightly hazy.

Two patients in the group treated during the first year showed toxic reactions. One was a white girl of nine months who on the day after the beginning of stovarsol treatment developed a temperature of 104°F . There were no associated findings and the temperature returned to normal the next day. On the day following the day of normal temperature through a misunderstanding the mother gave another dose of stovarsol and this time the temperature rose to 103°F . Gray powder was then given for two weeks after which stovarsol was again given and this time without reaction. The other patient in this group was a white boy two months old who was given 0.05 gm. of stovarsol for two days. He developed a temperature of 104°F and had a convulsion as reported by the neighborhood physician who cared for him and subsequently treated the syphilitic condition.

In three patients of this younger group it was doubtful that the patient reacted adversely to stovarsol. The first patient was a congenital syphilitic admitted to the hospital with bronchopneumonia, bilateral purulent otitis media, large spleen and liver and bone syphilis. Three days after treatment with 0.06 gm. of stovarsol daily he died. The second was a white infant of three months with bronchopneumonia, visceral and mucous membrane syphilis who was given 0.06 gm. of stovarsol daily for three days. Antisyphilitic medication was discontinued because he seemed very sick. He died three days later. There was no evidence that death was connected with stovarsol. The third patient in whom stovarsol had a doubtful toxic effect was a girl of six weeks with a bloody discharge dripping from her nose. The head was held retracted. There were scaling and infiltration of the inter-eyebrow region, a maculopapular rash, cylindrical-shaped chest and abdomen with marked retraction of the lower chest with each inspiration, the liver was firm and on a level with the umbilicus. The patient died after 0.06 gm. of stovarsol had been given for two days.

SEROLOGIC REACTIONS

Serologic response was very satisfactory. For purposes of comparison to the stovarsol treatment, we treated a group of 29 infants, beginning in the first year and continuing for one year, by the older methods of treatment, that is, with injections of mercury, bismuth, and the arsenicals, and gray powder by mouth. The same was done with a group of 48 patients in whom treatment was started after the first year of age and continued for one year. In the younger age group of 46 cases there were 35 treated with stovarsol for one year. Of this group 3, or 8 per cent, were positive at the end of one year of treatment. One in this group of 35 had negative serologic tests when first seen at seven weeks. Treatment was given to the child, however, because the mother had syphilis with very little prenatal treatment, and the child was pale, had snuffles and a palpable spleen. This leaves 3 out of 34 cases or about 9 per cent still positive. In 20 of these cases in which treatment was begun in the first year, reversal followed the first course of treatment, in 7 it followed the second course, and in 4 it followed the third course.

In this age group of the 29 cases previously mentioned, treated by the older methods of treatment, 18 or 62 per cent were positive after one year of treatment. These must not be considered Wassermann-fast cases, as many of them became negative in the second, third, or fourth years of treatment, and the same applies in the older age groups.

In the older age group of our series of 54 cases treated with stovarsol, 23 were not treated for as long as a year, leaving 31 cases. Three of the 31 cases, however, had negative serologic tests on the blood when treatment was begun, one of these three had a positive spinal fluid. Of the remaining 28 cases treated for one year, 16, or about 57 per cent, showed reversal following treatment, as compared to 80 per cent positive, or about 20 per cent, which showed reversal at the end of one year of a group of 48 cases treated by the older methods. As stated, these must not be considered Wassermann-fast, as many later became negative. In this older group a few had some little treatment before stovarsol was begun.

In this group of 28 older children treated with stovarsol, 5 patients became negative following the first course, 5 following the second, and 6 following the third course. By reversal we mean not only an entirely negative Wassermann test but also a negative Kahn test. Frequently the Kahn test was persistently one- or two-plus when the Wassermann was negative.

The patient with the positive spinal fluid and the negative blood tests is of sufficient interest to be detailed here. R. T., at about three and a half years of age, developed attacks of unconsciousness lasting fifteen to twenty minutes. These were two to three weeks apart. He had been treated in a neuropsychiatric clinic with

calcium lactate gr x, t.i.d. which seemed to free him of these convulsive attacks. However, he began to have severe spells of night crying which could not be explained by the parents. They were so prolonged that on several occasions the neighbors threatened to call the police. He was so irritable, quarrelsome and constantly on the go that he could hardly be managed at the nearby settlement house. He behaved in a similar manner at the dispensary. After several months it was learned that the parents had syphilis and were under treatment. The child was sent to us for a consideration of syphilis. We found a boy of four years and four months with a sallowish head with marked veins and prominent frontal bosses and suggestions of rhogades about the mouth. As stated the blood Wassermann and Kahn tests were negative but the spinal fluid Wassermann was acetone insoluble antigen one-plus, cholesterinized antigen two plus. The Lange colloidal gold test and the Pandy test were negative. The cell count was 15 mostly lymphocytes.

Treatment with stovarsol was begun and in a month the mother unsolicited reported that he was sleeping better and that he was much more easily managed. At the dispensary the child was tractable and quiet. Because we were dealing with cerebrospinal syphilis our dosage was increased to one fourth more than our usual full dose. After six months of treatment the spinal fluid was entirely negative and now after a year his general condition and behavior are excellent.

In one patient in the younger group treatment was begun at nine months of age. The general improvement was excellent but the Wassermann seems fast. That Wassermann fast cases occur also with the older type of treatment and even when treatment is begun very early is shown in the following case.

A boy three weeks old had mercury injections with alternate courses of sulphur sphenamine in full doses and gray powder by mouth for fourteen months. At the end of this time he had four plus Wassermann and Kahn tests. The family was dissatisfied because the serologic tests were not negative and took the child to a clinic where bismuth therapy was given. After a year they returned because the serologic tests were still four plus.

Improvement in the general condition of these patients is the rule. Their color improves rapidly and many gain markedly in weight. For example one child of two and one-half years gained 7 pounds in eight months, another, a girl of seven years three months who weighed 35 pounds when treatment was begun, gained 7 pounds in four months without change in regime. Condylomata disappeared in from one to two weeks. Interstitial keratitis responded more rapidly than usual, e.g., the first case detailed in the older children with toxic symptoms. Another was able to read two lines farther down on the chart for testing vision after four weeks of treatment. James¹ reports 7 cases of interstitial keratitis in which very satisfactory improvement was made with atovarsol. Hydrarthrosis and bone lesions responded very well. The improvement in one case of cerebrospinal syphilis is recorded.

SUMMARY

One hundred cases of congenital syphilis treated with stovarsol are surveyed. Serologic and clinical improvement was very good. Toxic

reactions to the drug occurred in from 5 to perhaps 8 per cent of the cases, and they were usually mild in character. Serologic reversal was very much better with stovarsol than with the older methods of treatment.

CONCLUSION

Stovarsol by mouth in rational conservative dosage, such as that of Bratusch-Marrain, is a valuable drug in the treatment of congenital syphilis.

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REFERENCES

- 1 Tuscherer, J. Monatschr f Kinderh 45 62, 1929
- 2 Bratusch-Marrain, Alois. Arch f Kinderh 92 26, 1930
- 3 Kiss, P. V. Jahrb f Kinderh 126 211, 1930
- 4 Mettel, H. B. Arch Pediat 48 761, 1931
- 5 Maxwell, C. H., and Glaser, J. Am J Dis Child 43 1461, 1932
- 6 Rosenbaum, H. A. Am J Dis Child 44 25, 1932
- 7 Abt, A. F., and Traisman, A. S. J PEDIATRICS 1 172, 1932
- 8 James, Wm. M. J Missouri State M A 30 33, 1933

CONGENITAL OSTEOSCLEROSIS

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CONSIDERABLE interest has been aroused in the study of bone changes in anemia as a result of the reports of Cooley, Witwer and Lee,¹ Vogt and Diamond² and others. In the condition described by these authors, there is a widespread bone change which apparently develops secondarily to a peculiar type of anemia. In the condition to be reported in this paper, an anemia is found associated with bone changes, but the relationship of cause and effect seems to be altered.

Albers-Schönberg,³ whose name usually identifies this disease, first called attention to the condition in 1904. Since that time, less than 40 cases have been described under a variety of different names. These include marble bones, osteosclerosis congenita, osteosclerosis fragilis generalisata, osteosclerotic anemia, osteosclerosis with various types of leucemia and osteopetrosis. Karshner⁴ has reviewed the literature to 1926 and gives abstracts of all cases reported together with a description of the clinical course and the roentgenologic findings. Prune⁵ has, more recently, described the progress of the disease as revealed by the roentgenogram in a series of cases which he has been able to follow over a period of twenty-one months.

The characteristic finding in congenital osteosclerosis is the roentgenologic demonstration of an overgrowth of the cortical portion of bone at the expense of the medullary cavity. The overgrowth is entirely endosteal and no enlargement of the bone occurs except in connection with the ends of the long bones where clubbing and deformity is frequently found. All bones of the skeleton are involved but the degree of involvement may vary in different parts. When the osteosclerosis is fully developed the roentgenogram reveals a dense, homogenous bone shadow in which no normal markings or evidence of normal bone structure can be discerned. This appearance is usually most evident in the bodies of the vertebrae, the central portions of the pelvis, the base of the skull and the ends of the long bones. The roentgenogram usually demonstrates striations in the flat bones parallel to the borders and transverse striations or bands of lessened density in the sclerosed areas of the long bones. In these bands, bone trabeculations can be seen, a fact which is taken to indicate the occurrence of remissions in the course of the disease.

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The secondary manifestations of the disorder are the most important. These include retarded growth, anemia with enlargement of the liver, spleen and lymph glands, hydrocephalus, optic atrophy, pathologic fractures, imperfect dentition and mandibular suppuration. The secondary manifestations are not constantly present but vary with the degree of involvement of the bones. The severe forms usually occur in childhood, usually show a fairly complete development of secondary manifestations and are progressively fatal.

The disease exhibits a distinct familial tendency in its incidence. Multiple cases in a single family have been reported by several authors. In four instances the condition has occurred in one of the parents as well as in the child^{6 7 10} but in most instances the parents have been normal^{8 9 10 11}.

It appears as though the disease has its beginning in fetal life. Prime reports a roentgenogram showing a fetus in utero which, from the density of the vertebrae, suggested a case of marble bones. He reports this child again, at the age of five years, as a definite case of marble bone disease. Three necropsies have been recorded in which osteosclerosis has been found in infants dying soon after birth.^{12 13 14} The condition is more frequently met with during childhood but has been recorded as late as fifty-eight years of age.¹⁶

The cause of the disorder is not known. Heredity, congenital osteogenetic defect, syphilis, chronic infection, endocrine disturbance involving any or all of the following glands, hypophysis, parathyroids, thyroid and thymus, and avitaminosis, all have been indicted by different authors as the cause. While the occurrence of the condition in association with endocrine disorders is frequent, heredity or a congenital defect in osteogenesis seems to be a logical interpretation of the etiology.

The pathogenesis of the condition is not understood. It would seem as though there must be an alteration in the calcium and phosphorus metabolism but, save for a few determinations, the blood chemical values for calcium and phosphorus have been found to be normal. Determinations of calcium balance have revealed an increased urinary excretion of calcium but no definite evidence of increased retention.¹⁷ The calcium content of the pathologic bone has been found to fall within normal limits. Kooylow and Runowa¹⁸ have shown a marked decrease in the phosphorus and an increase in the magnesium content of the pathologic bone.

As a part of the general retardation of growth, the development of centers of ossification is usually delayed and ossification of the cranial sutures is late. The interference with growth has been explained on the basis of dysfunction of the hypophysis. The osteosclerotic process in the skull produces marked changes in and about

the sella turcica. Frequently the sella is narrowed and a characteristic finding is thickening and clubbing of the posterior clinoid process. At necropsy the hypophysis is usually small.

The type of anemia found in these cases is not specific. It is brought about in the replacement of bone marrow by cortical overgrowth and does not differ from anemia produced by the replacement of bone marrow by tumor metastases or leucemic infiltrations. This type of anemia is usually termed osteosclerotic or myelophthisic anemia^{18, 20}. The characteristics of this anemia are as follows. There is a marked reduction in both the erythrocyte count and the hemoglobin content, making the color index slightly under 1. Anisocytosis and poikilocytosis are present and immature, nucleated red cells are usually found. Myelocytes and myeloblasts are present in the blood smear. The increase in the myeloid cells may bring about a leucocytosis though a leucopenia is not unusual. As a terminal manifestation, there may be a decrease in blood platelets and other characteristics of aplastic anemia. The severity of the anemia is dependent on the amount of bone marrow destroyed by cortical overgrowth but is influenced by the regenerative power of the remaining marrow and the degree of extramedullary hematopoiesis which may occur²¹.

Enlargement of the liver, spleen and lymph glands is a common finding associated with anemia. Pathologically these organs show a marked myeloid reaction with extramedullary hematopoiesis which might be considered a reversion to the embryonic type of blood formation. In one necropsy foci of hematopoiesis were found in the kidney¹⁶. The degree of metaplasia of the myelogenous elements may result in the production of a blood picture which resembles that of leucemia.

Bone changes occurring in the skull, while not limited to the base, are most marked in this area. The most remarkable point in connection with the sclerosis of the base of the skull is the narrowing of the foramina which is produced. Hydrocephalus has been noted, particularly in the younger patients and has been explained as arising from the circulatory disturbances produced by the narrowed foramina. A more important result of the changes at the base of the skull is the production of optic atrophy. Like hydrocephalus, optic atrophy is noted particularly in the younger cases, but the two phenomena are not always found associated. Optic atrophy is probably produced by pressure on the nerve as it passes through the narrowed optic foramen. Epistaxis may be a manifestation of pressure on the ophthalmic vein. Distortion of the orbital cavity may cause a slight exophthalmos. In many cases a nystagmus has been observed and interpreted as a result of sclerosis of the bony labyrinth.

The occurrence of pathologic fractures has often made possible the diagnosis of mild forms of the disease. The increased fragility which permits these fractures to occur belies the implied hardness in the descriptive term, "marble bones." Prime feels that the term, "chalky bones," better describes the condition. Karshner prefers the term, "osteopetrosis." Pathologic fractures have been found as early as four months of age, though they are more usual in later childhood and in adult life. A peculiarity of these fractures is that they occur at right angles to the shaft of the long bones, a feature attributed by some authors to decreased elasticity and, by others, to abnormal fragility at the points of the transverse bands of lessened density which the roentgenogram reveals.

As a part of the general disturbance, dentition is usually delayed and the teeth are imperfect. Dental caries is very common. A marked tendency toward the development of suppuration of the lower jaw has been noted. This process is probably a consequence of insufficient blood supply occasioned by pressure on the alveolar artery as it traverses its bony canal in the mandible.

The course of the disease is essentially chronic. The osteosclerotic process, per se, is not incompatible with life. The secondary manifestations constitute the serious menace to life. The severe forms in childhood are invariably fatal, death being due, early, to severe anemia and asthenia, while, later, suppuration of the lower jaw is usually linked with a fatal outcome. Goodall's patient died at ten weeks with a hemoglobin of 22 per cent, while the earliest death in a case in which suppuration of the jaw was present, occurred at five months. If the disease is not severe enough to produce serious secondary manifestations, the process may become arrested and the outlook, then, is fairly good. There is no known method of eradicating or arresting the osteosclerotic process.

There is no treatment which seems to have any effect on the disease. Treatment with a diet in which calcium is restricted seems to be of no value. The use of ammonium chloride has produced no tangible results. Zadek calls attention to the fact that irradiation of the long bones or spleen is contraindicated. Splenectomy, a procedure which also would seem to be contraindicated, has been performed without benefit. Pehu has advised a partial removal of the parathyroid glands. The little we can do is to endeavor to prevent the occurrence of fractures by guarding against trauma, to enforce strict dental hygiene to avoid dental infections, to supply iron salts and blood building preparations to combat the anemia and to avoid those substances which promote calcification.

The following patient presents the typical picture of congenital osteosclerosis.

CASE REPORT

N. Z., female Italian aged ten months, was admitted to the hospital on Dec. 24 1931, with the complaint of failure to gain. Both grandparents on either side had died from unknown causes at advanced age. One of the father's brothers had died at five years of age from a disease which had been present from birth, producing deformities of the legs. An accurate history of this illness could not be obtained. The father and mother of the patient were normal. There were no other children and there had been no other pregnancies. In 1923, the father had received treatment for a chancre. His blood Wassermann test had been negative, at that time, and on repeated examinations in intervening years.



Fig. 1.—Facies at 10 months of age.

The child had been born at full term by a difficult forceps delivery after a protracted labor. The birth weight was 6½ pounds. The newborn period was normal.

The infant had been breast fed for one month and was then changed to a modified cow's milk formula. From birth until three months of age, the child had been given 5 drops of viosterol three times a day. From three months of age until the time of admission to the hospital, she had received 3 teaspoonfuls of 10-D cod liver oil daily.

The child was able to sit alone at seven months. The first tooth appeared at eight months.

The parents had always noticed that the child was rather pale and that the pallor was increasing. She had never taken her formula well and had gained weight very slowly. About two months before admission, the infant had bled, a little from the nose over a period of four days. One week later this was repeated for a day. There had been no bleeding since that time. There had been no vomiting or other gastrointestinal symptoms.

Physical Examination The patient was a poorly nourished, poorly developed, female infant weighing 15 pounds and 2 ounces. The facies were rather peculiar, there was a marked pallor with a slight yellowish tinge, the expression was apathetic and rather mask like, the forehead was broad and high and there were prominent frontal eminences, the cutaneous veins were dilated, the eyes were widely separated and prominent but normally shaped, the bridge of the nose was very slightly depressed, the malar eminences were not prominent, the chin was small and receding, the entire face seemed a little puffy and prematurely aged.

The head measured 45 cm in its largest circumference. There was a peculiar stony consistency to the cranial bones. There were prominent bosses over the parietal bones with a depression along the sagittal suture. The anterior fontanelle



Fig 2—Roentgenogram of the skull showing increased density of all cranial bones especially marked at the base. The posterior clinoid process is clubbed.

was open about 2 cm and was slightly depressed. The bony edges of the fontanelle were firm and slightly everted.

There was a constant, fine, rapid nystagmus. Light perception was apparently present but no other evidence of vision could be elicited. Examination of the fundi showed a bilateral optic atrophy.

There was one tooth present. This had a white, chalky appearance.

The abdomen was full, particularly in the left upper portion. The spleen tip was palpable at the level of the iliac crest, the organ being very firm in consistency and smooth. The liver edge was at the costal margin. The inguinal lymph nodes were slightly enlarged.

There was no deformity of the extremities and there was no disproportion of these parts to the rest of the body.

Laboratory Findings

Red blood cells	3,480 000	Blood platelets	240,000
White blood cells	7,100	Bleeding time	4 minutes
Hemoglobin	60%	Clotting time	6 minutes
Polymorphonuclears	23%	Normoblasts	8 per 100 W B C.
Lymphocytes	40%	Reticuloocytes	0%
Mononuclears	15%		
Lymphoblasts	3%		
Myelocytes	7%		
Myeloblasts	3%		

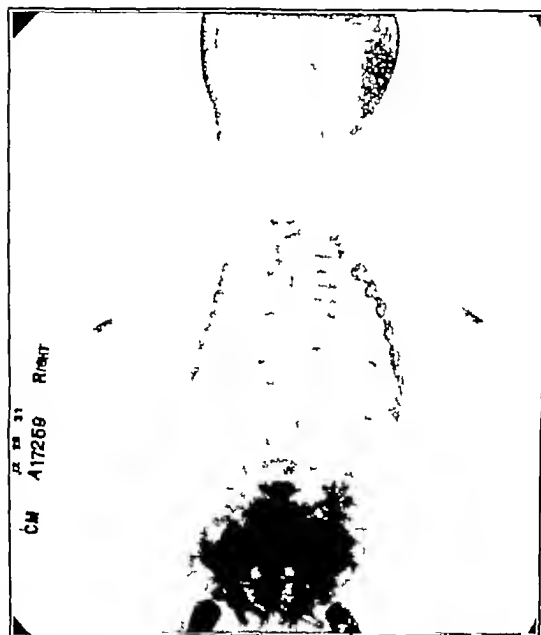


Fig. 3—All bones of the skeleton showed marked increase in density. In the upper extremity this is most marked at the ends of the bones.

Anisocytosis polkilocytosis and polychromatophillin present

Fragility test—hemolysis began at 0.52% and was complete at 0.40% (control—0.44 to 0.32%)

Blood Chemistry—N.P.N.—33.4 Sugar—87.8, Serum Chlorides—596 Calcium—10.1 Phosphorus—4.0 Icterus Index—11 Seroprotein—5.7 Albumin—4.1 Globulin—1.6.

Urinalysis including urobilinogen test was negative

Blood Wassermann tests on the patient and both parents were negative

The diagnosis was made by roentgenologic examination. The following report was made by Dr. A. L. L. Bell

"The skull appears to be of moderate size. The suture lines are normally outlined. All of the bones of the vault and also those of the base are slightly thickened and unusually dense, with a rather marked obliteration of the normal bony architecture and bony trabeculations. The sella turcica is faintly demonstrated and appears to be moderate in size and normal in outline. There is marked increased calcification noted in the clinoid processes which show obliterated bone texture.

"The remainder of the skeleton, including the vertebrae, thorax, upper and lower extremities, and pelvis, all show similar changes. These changes are also noted in the epiphyses. In the long bones, especially in the upper extremities,

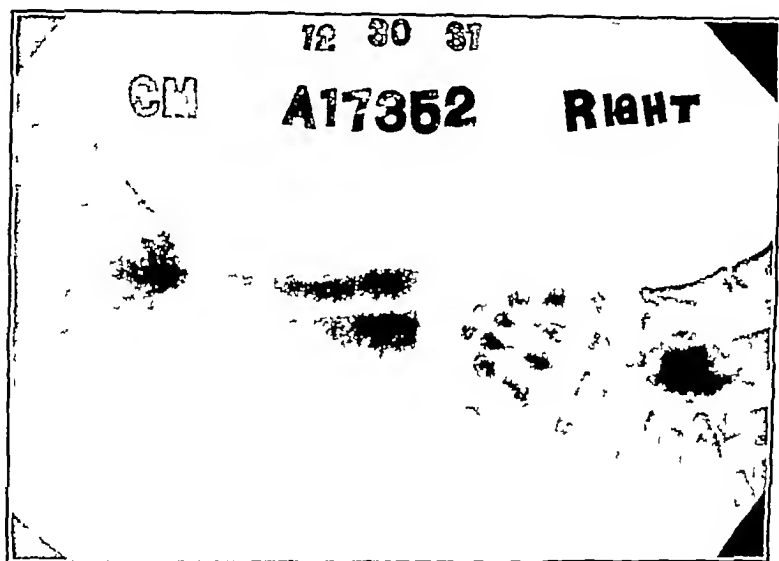


Fig 4—In the bones of the forearm transverse striations can be seen near the epiphyses. The bones of the hand show hour glass areas of increased density.

the mid portions of the shaft show some normal bone trabeculations but in the epiphyseal portions of the shafts on either side there is marked obliteration of the normal bone texture and marked calcification. This is demonstrated to a lesser extent in the bones of the hand."

"Conclusion 'Marble Bones' "

The child remained in the hospital for twenty four days. Two small transfusions were given. Ammonium chloride was given in doses of 5 grams per day. An attempt was made to limit the calcium intake but considerable difficulty was experienced with the administration of solid foods, making it impossible to eliminate milk from the diet. Repeated blood studies showed immature cells in the normoblastic, myeloblastic and lymphoblastic series, with a total white count gradually rising from 7,000 to 15,000. There was a noticeable increase in the size of the spleen and the liver became palpable to 2 cm below the costal margin. She was discharged from the hospital with a hemoglobin of 70 per cent.

One month later the child was readmitted to the hospital with a hemoglobin reading of 55 per cent red cell count of 3,160,000 and white cell count of 23,500. There had been little change otherwise in the general condition.

During the year following this the child was seen infrequently. There was a progressive enlargement of the liver and spleen a gradual increase in the anemia, poor weight gain retarded growth and frequent attacks of epistaxis.

The last examination was made at 23 months. About a week prior to this, the child had had a severe epistaxis.

The head measured 46.4 cm. in circumference. The anterior fontanelle was closed and there was a bony bulge in this region. There was a slight exophthalmos. Seven teeth were present all presenting a flat chalky white appearance. The alveolar margins were tremendously thickened so that the arch of the palate was represented by a groove about 1.5 cm. in width and depth. The abdomen measured 55 cm. in circumference. The liver edge was 3.5 cm. below the costal margin. The spleen filled the entire left half of the abdomen the tip being in the pelvis and the body of the organ producing a bulge in the flank. Epiphyses were slightly enlarged. There were two small purpuric spots on the right leg.

The hemoglobin was 34 per cent, the red cell count 1,880,000, the white cell count, 49,800, the platelets, 110,000. Bleeding and clotting times were normal. The stained smear presented a most bizarre picture. The differential count was polymorphonuclears, 29 per cent myelocytes 15 per cent myeloblasts 10 per cent lymphocytes, 32 per cent lymphoblasts 8 per cent monocytes 5 per cent, eosinophiles, 1 per cent nucleated red cells, 14 per 100 WBC reticulocytes 15 per cent. Fragility test—hemolysis began at 0.48 per cent and was complete at 0.82 per cent (control 0.44 per cent to 0.28 per cent). The blood calcium was 9.0 mg. per 100 c.c. and the blood phosphorus was 2.9 mg. per 100 c.c. The icterus index was 8.

Since this examination the chief feature of the child's course has been repeated attacks of severe epistaxis, occurring at weekly intervals but without other purpuric manifestations. In spite of the marked anemia the child recently survived a severe upper respiratory infection.

COMMENT

The striking feature in the history of this case is the large amount of vitamin D which the child received. The idea that osteosclerosis may represent the extreme in the healing of a rachitic process has been advanced but is generally discounted since rachitic changes have not been demonstrated in these cases. The administration of vitamin D may accelerate the progress of the condition. In this connection the blood chemistry is of interest. Both determinations of phosphorus have given low values, the second determination after thirteen months without added vitamin D in the diet giving a value suggestive of active rickets. It is difficult to reconcile this last determination with an increased rate of calcium deposition. Though roentgenologic evidence is lacking it may be that the disease process is in a stage of remission.

The entire subject of the relationship between bone changes and blood changes is probably much more complex than this presentation would seem to indicate. The possibilities that bone changes in this condition are secondary to or simultaneous with bone marrow changes

was assumed that those animals which produced a milk of low curd tension in the second month of lactation would continue to do so throughout the major part of the remainder of their lactation period. This assumption proved to be erroneous, for it was found that some of those animals, chosen early in March as producers of soft curd milk had changed by April 1 to producers of milk of medium hard curd, necessitating their being discarded. Moreover, throughout the period from April 1 to October it was necessary to replace certain animals with others because of the change in the curd tension of their milk. It was planned to furnish milk of a curd tension below 30 grams, but in reality during certain short periods the tension increased to 30 to 35 grams or even higher on occasion before the individual cow responsible for the increase could be replaced by another of lower tension.

The cows chosen were healthy, nonreactors to tuberculin and abortion tests, and were included in the two-time string. It was planned to furnish the mixed milk of not less than three animals. In all, nine animals were used—6 Holstein-Friesian and 3 Ayrshires. To insure a milk of good quality both from the standpoint of bacterial content and of flavor, not only were the utmost precautions taken from the sanitary standpoint but also feed was withheld from the animals during the five hour period previous to milking. That the count for the total period showed a maximum of 11,000 per c.c., a minimum of 1,000, and an average of 5,100, and that the milk was of excellent flavor at all times, bespeaks the care of handling and producing.

The milking was done in mid-afternoon, the supply was immediately cooled, bottled, packed in ice containers, and shipped immediately to its destination in San Francisco. One man was responsible for this phase of the study throughout the period. Samples were analyzed chemically daily, were scored for flavor daily, and were examined for bacterial count at least weekly.

Table I summarizes by months the results of the daily chemical analyses. Fat percentages were obtained by the Babcock method, and total solids gravimetrically using the Mojonnier machine, the solids not fat being determined by difference. Casein and total protein were determined using the formaldehyde titration method. It was felt that this method was sufficiently accurate for the routine daily analyses, especially where comparative values were desired. In the determination of ash the standard procedure was employed.

The sole purpose of determining the coagulability by rennin and the P_{H} value of the milk was to indicate that it was normal milk. Physiological disturbances in the cow have been found to be reflected in these values as definitely as such indices as changes in body temperature, for instance. The rennin coagulation values were determined using a 2 per cent concentration of rennin and temperature of $39.5^{\circ} C$. The P_{H} values were determined electrometrically using the Type K Leeds and Northrop Potentiometer and Bailey type hydrogen electrode. The rennin coagulation and P_{H} values clearly indicate that the milks used throughout the study were normal for cow's milk.

The curd tension values were determined using a modification of the method described by Hill.² The curd knives were exactly 2 inches in diameter, a Chatillon's improved spring balance was used to measure the tension, but instead of using the

TABLE I
MONTHLY SUMMARY OF THE ANALYSES OF DAILY SAMPLES OF LOW CURD TENSION MILK¹

DATE	CURD TENSION GRAMS	FAT PER CENT	SOLIDS NOT FAT PER CENT	TOTAL SOLIDS PER CENT	CASEIN PER CENT	PROTEIN PER CENT	ENERGY CALORIES PER KG	ASH PER CENT	COAGULATION TIME	RENNIN
	Max.	3.89	8.40	11.83	2.45	2.95	690		3 45"	0.69
	Min.	3.17	7.48	10.04	2.00	2.42	0.17		4 48"	0.63
	Ave.	3.40	7.90	11.35	2.25	2.73	0.40		5 20	0.66
Reported analyses†		3.13.50	9.00	12.46		3.25	690			
	Max.	4.16	8.3	12.13	3.21	3.63	705	0.716	3 30	0.65
	Min.	3.0	7.63	10.93	1.95	2.23	600	0.003	3 20"	0.72
	Ave.	3.57	7.00	11.47	2.06	2.49	657	0.700	3 00	0.73
Reported analyses		3.43.59	9.00	12.40		3.3	690			
	Max.	4.40	8.44	12.47	2.29	2.70	713	0.710	4 30	
	Min.	2.90	7.36	11.07	1.93	2.43	603	0.703	4 28	
	Ave.	3.72	8.10	11.70	2.14	2.38	676	0.700	4 29	0.61
Reported analyses		3.72	8.06	12.08		3.31	710			
	Max.	4.80	9.19	12.89	2.44	2.94	793	0.722		
	Min.	3.50	7.48	10.80	2.20	2.63	633	0.671		
	Ave.	3.96	8.21	12.13	2.31	2.78	709	0.697		
Reported analyses		3.90	9.10	13.00		3.27	734			
	Max.	4.60	9.02	13.39	2.37	3.09	802	0.710	6 13	0.67
	Min.	3.80	8.14	12.18	2.21	2.60	696	0.680	4 57	0.65
	Ave.	4.20	9.48	12.74	2.40	2.81	744	0.698	5 42	0.63
Reported analyses		4.25	0.68	13.03		3.63	703			
	Max.	4.00	8.6	13.33	2.62	3.15	800	0.099	0 11"	0.60
	Min.	3.30	7.87	11.28	2.05	2.40	684	0.074	5 10"	0.64
	Ave.	4.19	8.23	12.44	2.32	2.79	728	0.687	3 30"	0.67
Reported analyses		4.11	0.41	13.33		3.69	777			
	Max.	4.90	8.18	12.60	2.40	2.89	770		5 30	
	Min.	3.24	7.72	11.18	2.00	2.41	631		4 17"	
	Ave.	3.81	7.06	11.70	2.10	2.61	650		5 05	
Reported analyses		3.81	0.03	12.84		3.20	725			

¹Analyses made by N. P. Tarasank and Miss M. A. Ashenfelter

Calculated on basis of 4,230 Calories per pound fat and 1869 Calories per pound solids not fat (III) (gr Exp. Sta. Bull. No 308 1928)

†Kahlenberg and Vork. Jour Agr Research 43; No 8, p. 761, 1931 Table II.

mayonnaise jar, special jars $2\frac{3}{16}$ inches in diameter having flat bottom and straight sides were procured. Cut off rain gauges were found very satisfactory. For the coagulant, rennet extract was found not only to yield results very similar in value to the pepsin calcium chloride mixture described by Hill, but also gave less trouble in securing duplicate readings and less "piling" with certain milks. Fresh rennet was kindly furnished monthly by Chr. Hansen's Laboratory, Inc. When kept cold these samples were found to decrease only very slightly in strength during the month. One c.c. of rennet extract was quickly added and stirred into 100 c.c. of milk. Clotting in the case of unheated milk is almost instantaneous. Since 37.5°C is not only closer to the optimum temperature for rennin coagulation, but also more nearly approximates body temperature than 35°C , it seemed desirable to employ the former temperature during the rennin action. This was followed during the month of April. However, because the curd test at the higher temperature is a few grams higher than at the lower, in order that these tests should be comparable with those already reported, it was decided to employ the lower temperature throughout the remainder of the study.

TABLE II
CURD TENSIONS OF VARIOUS FORMULAS

RAW LOW TENSION MILK OZ	KARO TBSP	WATER OZ	CURD TENSION		
			RAW GRAMS	BOILED 3 GRAMS	BOILED 10 GRAMS
14	2	—	27	13	13
15	2	—	30	13	12
16	2	—	32	10	6
16	3	—	19	3	1
18	3	—	28	13	7
20	3	—	36	11	11
14	2	10	8	7	7
15	2	9	10	6	6
16	2½	8	8	9	10
18	3	6	14	7	7
20	3	5	17	11	9
RAW CERTIFIED MILK	KARO	WATER	RAW	BOILED 3'	BOILED 10'
14	2	—	38	5	3
15	2	—	40	9	7
16	2	—	58	9	9
16	3	—	46	7	4
18	3	—	35	11	10
20	3	—	45	10	10
14	2	10	16	7	6
15	2	9	17	6	9
16	2½	8	23	8	9
18	3	6	27	10	10
20	3	5	31	11	9
EVAPORATED MILK*	KARO	WATER	RAW	BOILED 3	
Blank	—	—	4	4	
15	2	—	3	3	
15	2	9	3	3	
RAW MARKET MILK†	KARO	WATER	RAW	BOILED 3'	
Blank	—	—	87	14	
15	2	—	73	9	
15	2	9	28	7	

*Reconstituted 1:1 Final analysis: Fat 3.0% S N F 10.32%
†Random sample Fat 4.4% S N F 8.97%

In making the tests reported in Table II, in which the effects of dilution, addition of syrup and heating were studied it was necessary to add calcium chloride to obtain rapid clotting especially in the heated samples. Hence, the unmodified Hill test, excepting the jars was employed throughout that series of observations.

In making the readings the balance was mounted in a vertical position over a movable platform. The jar with its contents was placed on the platform, the balance was attached to the knife and the platform was slowly and carefully lowered until the knife was drawn through the curd.

That there were considerable fluctuations in the composition of the milk from time to time is indicated by the wide differences in maxima and minima (Table I). As stated before precautions were taken to guard against this occurrence especially in connection with the selection of animals their care feed, and the handling of the milk. Frequent tests of the milk from the individual cows, however showed definite variations, making it necessary to replace certain animals with others or in making up the supply of mixed milk to use only a minimum quantity of the milk of that animal yielding milk of highest curd tension. The maximum values therefore, appeared as seldom as possible throughout the period, usually not over two or three times in any one month. Changes in climatic conditions unquestionably played an important rôle in inducing variation in the percentage composition of the milk.

While as yet no well-defined quantitative relationship can be established between the curd tension and the percentage composition of the milk, yet the fluctuation in the latter (Table I) is usually reflected in the fluctuation of curd tension. The term 'soft curd' is as yet not uniformly defined, but it is felt that the milk used throughout this study with the exception of those few samples already referred to is representative of 'soft curd' milk.

Little comment needs to be made in connection with the fat content of the milks, but inspection of Table I reveals that the average percentages of solids not fat are considerably below what are considered normal for the breed for the corresponding fat content. This is quite apparent when one compares the average values for each month with the analyses reported by Kahlenberg and Voris on the milk from 12 Holstein Friesian cows over the entire lactation period. It may also be observed that the concentration of protein in this low-curd tension milk is low when compared with that of the mixed herd milk of similar fat content.

From the nutritional point of view it is to be expected that milk whose major constituents (or any of whose major constituents) are lower in concentration than in mixed herd milk would be lower in energy value. That this is true is apparent when one compares the calculated energy values of the monthly average with those of herd milk of similar fat content. It will be seen that the milk of low curd tension

on the average was from 5 to 6 per cent lower in energy value than the herd milk. This was significant in compounding formulas for infant feeding as will be seen later (Clinical Study).

While there was considerable variation in the percentage of ash in the milk, yet the average values approximate closely those accepted as normal for the breed. From the nutritional aspect, little or no significance would be attached to this variation since it is known that cow's milk is abundantly rich in mineral constituents, and that the elements, calcium and phosphorus, are almost universally present in a constant ratio. It is recognized, however, that the mineral constituents do play an important rôle in connection with the buffer capacity of milk, especially as regards acidification.⁶ Electrometric titrations were made on representative samples of this low tension milk, and buffer curves were drawn. Buffer index values vary according to the P_H at which they are determined, but it was considered that the buffer capacity from the original P_H of the milk to a P_H nearing that of an infant's stomach at the height of digestion might be of some value clinically. Gonce and Templeton⁷ have indicated that the latter value approximates P_H 3.75. Our buffer curves indicate that the buffer capacity of cow's milk is greatest between a P_H of 5.2 and 5.7 which is in agreement with that recently reported by Holm, Webb and Deysher.⁸ For the sake of comparison with the results of the latter workers, the average buffer capacity from the original P_H of the milk to P_H 4.7 was calculated. The value of 0.0191 for the low tension milk, 0.0211 for the milk of two normal Holstein-Friesian cows, and 0.0196 for milk admittedly low in buffer capacity, the latter two values being reported by Holm, Webb and Deysher, indicate that this low tension milk is considerably below the normal milk of the breed in buffer capacity. A further comparison, shows that, whereas it required 52 c.c. of tenth normal hydrochloric acid per liter to reduce the P_H of the normal Holstein milk from the original P_H to P_H 4.7, only 46 c.c. were required to effect a similar change in the low tension milk. Similar differences would be expected if the acidification were continued to P_H 3.75.

Table II illustrates what is to be expected when various feeding formulas, with and without heat treatment, are subjected to the curd test. The heating was done over a rapid electric heater, and excessive loss of moisture was prevented by the use of an air condenser. Kari itself appears to have little or no effect on the curd tension of raw milk, while dilution, as is to be expected, exerts a pronounced lowering, especially at the dilutions greater than 10 per cent. The effect of heat on the proteins of milk is reflected very distinctly in the marked lowering of the curd tension by the boiling for 3 minutes and 10 minutes, the longer period of heating having little or no advantage over the shorter. The effect of boiling is increased with increased concentrations

of Karo, due in all probability to the increased boiling point of the mixture. In the case of the reconstituted evaporated milk neither dilution nor heating exerts an appreciable effect on the curd tension.

CONCLUSIONS

1 Although different cows are known to secrete milk of varying curd tension, it has not been our experience that an individual cow invariably continues to secrete milk of a uniform curd tension throughout the major portion of her lactation period.

2 The prevailing opinion that normal milk of low curd tension is low in solids not fat, notably in proteins, has been confirmed.

3 Normal milk of low curd tension is low in energy value.

4 The buffer capacity of normal milk of low curd tension is less than that of milk of average composition.

5 Milk of low curd tension may be entirely normal with regard to physicochemical properties such as rate of rennin coagulation, and P_{H} as well as in bacterial flora.

6 The heat treatment accorded the various formulas in connection with infant feeding is effective in producing a mixture of very low curd tension, at least as far as average market milk is concerned. Prolonged boiling appears to have little or no advantage over the shorter period. The heating of mixtures in which evaporated milk replaces the raw milk is not effective in lowering the already very low curd tension of the mixture.

PART II CLINICAL APPLICATION

The feeding of infants on the soft curd milk was carried out in the nursery for newly born at the University of California Hospital and at the Babies Aid Foundlings Home. Both institutions are located in San Francisco. While the period of observation in the nursery was relatively short many of these babies are discharged as foundlings to the Babies Aid where they may remain for some time awaiting adoption. One of us (M.M.) being in charge of the latter institution observations in both institutions could be made by the same physician over a group of infants for a period of six weeks to six months. Infants not born in the University Hospital but admitted to the Babies Aid were also given this special feeding. The age on admission of this latter group varied from six days to two months. These infants were under observation for two to eight weeks. Under the physician's guidance the same nurses aided in making certain observations as they weighed, fed, and cared for these babies. It was felt that this arrangement made for much more reliable and uniform conditions than would obtain in the average clinic or outpatient department. It was also obvious that in contrast with the group reported by Elias our age group was limited to that important period in infant feeding under eight months. Included in the study were

babies whose initial feeding had not been under our direction, whose inheritance was not the best and whose environment had been poor. The variation in birth weight and lowered resistance to infection must be considered in reference to conclusions. Comparison, however, is made with much the same type of baby fed on evaporated and certified milk formulas.

We observed 60 babies on soft curd milk, but as brought out previously, the length of observation varied considerably. To make our results of any value we secured the help of a trained statistician. At her suggestion it was decided not to include the findings during the first week in the eleven cases which were put on soft curd at birth. The small number of calories consumed the first few days, and the initial loss of weight, were elements which would affect our conclusions. The

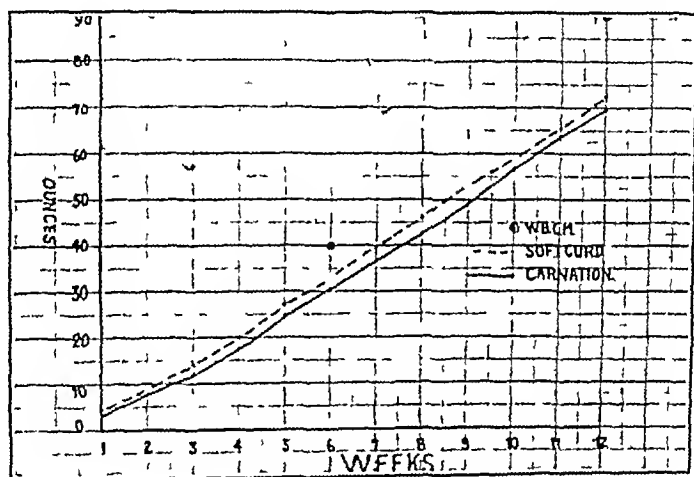


FIG 1

observations during the first week of life on babies started on soft curd milk before the eighth day have therefore been discarded in order that these cases might be included in this statistical study. For this same reason the cases followed longer than 56 days were also omitted as the number was so small that the statistical data would be rendered unreliable. These statistical studies have consequently been limited to a consideration of 44 cases observed over a seven week period. In our histograms for comparison these regulations were also taken into consideration.

The average age of the start for infants fed on soft curd milk was 177 days with an average weight of 7 pounds, 6½ ounces. That of infants fed on evaporated milk was 199 days with an average weight of 7 pounds, 9 ounces. Therefore, on the whole, these children had recovered their birth weight. (Fig 1)

DISCUSSION

The graph in Fig 1 shows a slightly greater constant gain, for infants fed on soft curd milk than for those fed on evaporated milk. Although our data on undiluted boiled certified milk covers the period

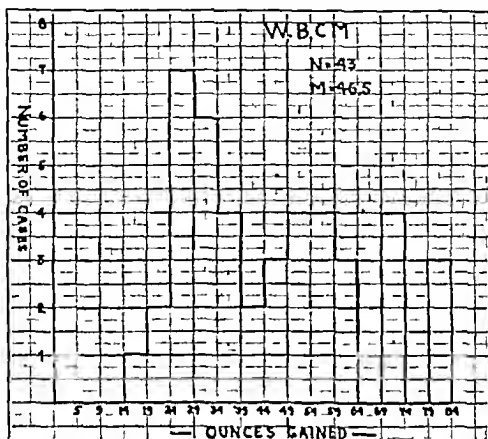


Fig. 1 Graph 1

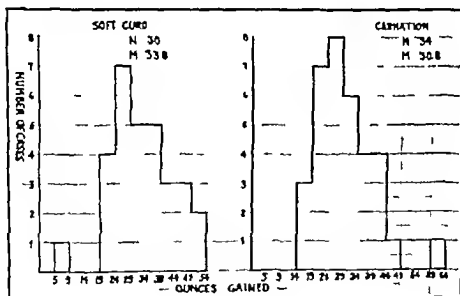


Fig. 2. Graph 2.

including initial weight loss, which is not included in either of the other groups and is hardly comparable, the gain in weight for the babies thus fed was much greater than for those fed on either soft curd or evaporated milk. The apparent difference in the gain of weight, of infants fed on soft curd milk over those fed on evaporated milk, has

been tested statistically by the standard deviation of the difference of means. It was found that this difference is insignificant, because the expected difference is greater than the observed difference.*

The histograms (Fig 2) of the distribution of the total gain of weight on the different formulas are offered for comparison, although as was mentioned previously, our series on the undiluted boiled certified milk formula is not altogether comparable, as it includes the initial loss of weight after birth (Fig 2, Graph 1)

From these histograms of weekly gain distribution the following are to be observed

1 A very good distribution of weekly gain in weight by infants fed on both soft curd and evaporated milk

2 A slightly greater constant gain for infants fed on soft curd than for those fed on evaporated milk

3 The range of variation for evaporated milk babies is apparently less than it is for infants fed on soft curd milk

4 With the exception of one case fed on soft curd milk there were no losses after the fourth week for either type of feeding

5 An interesting observation is that eight cases or 18 per cent out of 44 infants fed on soft curd milk showed a loss of weight during some one of the six weeks, and that 14 babies or 33 per cent out of 42 evaporated milk fed infants showed a similar loss

From a clinical point of view the infants on soft curd milk gained as well as a similar group on evaporated milk, but not as well as those on undiluted certified milk. The gain was usually gradual, and consistent. It was exceptional if a loss was incurred after the child was well started. However, from our clinical experience in infant feeding the group as a whole impressed us as being consistently hard to start artificially, when one took into consideration weight, comfort, and satisfaction. The babies were always hungry until they received from 42 to 95 calories per pound of weight or an average of 58 calories. It was the exception for a patient to be satisfied before receiving from 2 to 3 ounces of milk per pound of body weight. To make up the calorie intake necessitated adding from 8 to 11 per cent of carbohydrates. This increased requirement was also noted by Elias. It may also be explained by the lower energy value as reported in Part I. An added reason for this higher feeding might also relate to the more frequent and copious stools. The average number of stools was from 4 to 6 a day, always soft and voluminous. They had the characteristics of a mother's milk stool, like scrambled eggs with soft fat curds. These, however, became smoother in consistency as the baby became accustomed

*The real difference is 33.8 minus 30.8 which equals 3 and the square root of the difference of these means is 5.54. Therefore, the difference in the variation around the mean as great as this could be expected within the realm of probability. i.e., in any series of cases under similar conditions one might expect to find as great a variation as was found in these cases.

to the formula. Contrary to the results of former observers the majority of our babies or 79.1 per cent, passed large protein curds in the stool at various times although their discomfort seemed in no way related to the passing of these curds. Regardless of the increased number of stools and the amount of carbohydrates in the formula, excoriation of the buttocks was not observed.

In the beginning we felt that these babies had more gas than the certified milk infants this being the reason for their discomfort. As our experience increased and the infants were given more to eat, this discomfort diminished and gas became a negligible factor. It has been claimed that because the curd of low tension milk is soft and flocculent it is possible to give this milk undiluted and unboiled to the youngest baby, even to a weak premature baby. This may be a fact, but it is surprising how long the average baby took to accommodate himself to this milk, three weeks often passing before he was satisfied. We have fed about equal numbers on diluted and undiluted formulas, 22 of the former and 18 of the latter and find no appreciable difference. This is somewhat surprising if curd tension is so large a factor in the digestibility since dilution reduces still further the curd tension of milk (see Table II). Four of the babies who failed to gain and were unhappy on undiluted milk became comfortable and immediately gained when the same formula was diluted. Our intention was to use only unboiled milk but on losing two babies after a 24-hour illness, sixteen cases were put on boiled diluted milk. The babies taking this formula were happy and satisfied and gained as well as the babies of the other two groups. It might be of importance to note that the stools in this group numbered only one to three a day and were much firmer and smoother.

The impression regarding tissue turgor was that babies who did well on soft curd milk invariably had hard and firm tissues. This might be due to the relative amount of lactalbumin which is theoretically of greater nutritional value. (See Table I.)

SUMMARY

A group of 60 infants ranging from birth to six months of age were fed on soft curd milk for a period of time ranging from 2 to 8 weeks. For statistical study the results of 44 infants thus fed and observed over a seven week period were compared with results in similar groups fed undiluted boiled certified milk and diluted evaporated milk formulas. Histograms are presented for graphic comparison. When fed to the point of satisfaction, infants require more soft curd milk than ordinary cow's milk, due probably to the lower energy value of the former.

Clinical impressions suggest that while not superior to other accepted formulas soft curd milk is difficult to start, but when well started is

very satisfactory and results in excellent tissue turgor. The stools of infants on soft curd milk are more frequent than those of boiled, diluted cow's milk and may often contain large casein curds.

CONCLUSIONS

Considering (1) the variability in the production of soft curd milk and the increased observation necessary in its production, (2) the lack of superior results when used in comparison with other accepted infant formulas, soft curd milk does not warrant special production and certification for use in infant feeding.

REFERENCES

- 1 Buckley, S. S. Maryland Agr. Expt. Bull. No. 184, 1914.
- 2 Washburn, R. M., and Jones, C. H. Vermont Agr. Expt. Sta. Bull. 195, March, 1916, Burlington, Vt.
- 3 Espe, D. L., and Dye, J. A. Am. J. Dis. Child. 43: 62, 1932.
- 4 Hill, R. L. Utah Agr. Expt. Sta. Bull. 227, 1931.
- 5 Elias, H. L. Am. J. Dis. Child. 44: 296, 1932.
- 6 Associates of Rogers. Fundamentals of Dairy Science. The Chemical Catalogue Co., N. Y., 1928, p. 124.
- 7 Gonce, J. E., and Templeton, H. L. Am. J. Dis. Child. 39: 265, 1930.
- 8 Holm, G. E., Webb, B. H., and Deysher, E. F. J. Dairy Science 15: 331, 1932.

POSTVACCINAL ENCEPHALITIS

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HISTORICAL

IN 1905, Comby of Paris reported a case of encephalitis following vaccination. In 1912 another case was reported in the London Hospital. Mader reviewed a case observed in Germany in 1912. Lucksch of Prague in 1924 called attention to cases of supposed epidemic encephalitis following antismallpox vaccination. In 1924 Bastiaanse of Holland observed his first case. Five similar cases were observed elsewhere in Holland in the same month. In February, 1929, Wirsmann of Denmark reported 11 cases of severe cerebral disturbances following vaccination. In the same month Levaditi of the Pasteur Institute Paris reviewed over one hundred cases occurring up to that time in Europe. The most severe outbreaks have arisen in Holland and England.

From the report of the Smallpox and Vaccination Commission of the International Office of Public Hygiene¹ the following more recent data concerning the distribution of postvaccinal encephalitis were obtained.

During 1923-1927, 139 cases of disease of the central nervous system following vaccination were described in Holland, of which 41 patients died. Many new cases have been reported since then. The ratio for the years 1923-1927 was one case to five thousand vaccinations with a fatality of one in three. For the first six months in 1928 the proportion was one case for each twenty-eight hundred vaccinations. For a period of five weeks a vaccine from a country in which no case of postvaccinal encephalitis had been reported was used. A case occurred, however, with this lymph in spite of the small number of vaccinations. The available data for England totaled about 130 cases. The ratio was one for forty-eight thousand vaccinations.

The report of a Commission in Germany covers a total of 102 cases. During the four-year period under consideration for each million persons vaccinated the first time there were nineteen disorders of the nervous system following the vaccinations with seven deaths. For each million persons revaccinated there was only one disorder of the nervous system with a fatal issue.

Sixty-five cases were reported in Austria. Twenty of these occurred in Vienna alone among 39,000 vaccinations. Twenty-nine cases occurred in Norway, 13 cases in Sweden, several cases in Czechoslovakia, a few cases in France and Switzerland, two cases in Soviet Russia, one case in Portugal, and one case in Yugoslavia. No cases occurred in Belgium, Spain, Greece, Italy, Poland, and Rumania. One

case has been reported from Canada, and one from South America since the report of the Smallpox and Vaccination Commission of the International Office of Public Hygiene

The wave of this serious complication of vaccination began to recede gradually during the year 1929. References in the literature to new cases during the years 1930-1932 are scanty.

According to the delegate from the United States, as reported at Session of May, 1930, of the Permanent Committee of The International Office of Public Hygiene,¹ the total number of cases in the United States was about 20. Armstrong² states that 71 cases were recorded in the United States during the past ten years. Gordon and Rhea³ recorded a case of postvaccinal encephalomyelitis in July 1932. Rochm⁴ reported a case in December, 1932, which he had observed in September, 1930. My own case, which occurred in February, 1930, is reported for the first time in this article. This would make a total number of 74 reported cases for the United States.

It is now thought that serious nervous complications of antismallpox vaccination have occurred in the past without having been recognized as such. In Germany an attempt has been made to reconstruct a great many such cases from the clinical and mortality records of vaccination cases. Some cases of postvaccinal encephalitis in the past are now believed to have been mistaken for tetanus.

ETIOLOGY

Since antismallpox vaccination constitutes the keystone in the arch of preventive medicine, one would expect a great deal of research and speculation on the cause of such a serious nervous complication as postvaccinal encephalitis and myelitis.

The early cases in Holland and in other continental countries occurred at a time when epidemic encephalitis was prevalent. It was thought that localization of the virus in the cerebral tissue inhibits the defensive power of the latter. This inhibition may unleash an encephalitis of the epidemic type in carriers or persons who already have a latent phase of the disease. It is a well-known fact that vaccine virus has a peculiar affinity for nerve tissue. Vaccine virus was demonstrated in the brain tissue in patients with encephalitis and also in patients who did not develop encephalitis.

Research by many investigators proved that the vaccine virus itself is not the cause of encephalitis. A neurovaccine, consisting of an emulsion of smallpox virus cultured *in vivo* in rabbits' brains, was used extensively on thousands of children in Spain without a single case of postvaccinal encephalitis. In Holland, one hundred and ten different kinds of lymphs were used and cases of encephalitis occurred after forty one of these.

The Committee appointed by the Minister of Health and the Medical Research Council in England, under the chairmanship of Sir Hum-

phrey Rolleston, to report on the preparation and standardization of lymph, methods of diminishing or removing the risk of vaccination, and the best method of protection does not incriminate any particular lymph. However, it is held that the vaccination virus, whatever its past history, and in whatever medium incorporated, initiates the nervous disturbance. A local individual predisposition to nervous disorders—in the widest sense of that term—is responsible for the unpleasant sequel to vaccination. This is as far as the British report goes.

An observation published later than the British report would seem to strengthen the theory that a local individual predisposition is responsible for postvaccinal encephalitis. Reisch⁵ observed 2 fatal cases of postvaccinal encephalitis showing the characteristic histologic picture. During life these patients had myoclonia affecting most of the voluntary muscles. A careful investigation of about 300 children in the same neighborhood revealed the presence of myoclonia in many and in both the vaccinated and unvaccinated children to an equal extent.

Netter who has thoroughly studied this question discussed this subject before the Academy of Medicine in Paris.⁶ He disregards the conception of some authors that a contaminated vaccine might be the cause of the encephalitis and likewise, the views of others, who assume that a virus existed previously in the brain of the subjects and was enhanced in virulence by the vaccine. He contends that it is a question of an attack on the brain by the vaccinal virus which can occur only in subjects with a nervous system that is particularly susceptible, and with a very active vaccine.

In 1927, when postvaccinal encephalitis occurred in alarming frequency in Holland the law which decreed compulsory vaccination was temporarily revoked and a committee was appointed to study the cause of this complication and the ways to combat it. The Committee published a report in 1932 which contains a thorough survey of encephalitis postvaccinalis.⁷ Several hypotheses have been investigated but no solution to the problem has been found. Encephalitis occurred with all kinds of lymph. Animal experiments to produce postvaccinal encephalitis failed.

In the discussion of the etiology two hypotheses are especially stressed. First that the condition is due to the activation of a latent virus. Second that the vaccine virus itself causes the disease. Neither can be regarded as proved. With this it seems, our present knowledge concerning the causation of postvaccinal encephalitis rests.

Leiner of Vienna advanced the theory that encephalitis following vaccination was due to cerebral metastases. Weichsel⁸ cites a case in a child aged eighteen months who developed a generalized vaccinia and encephalitis nineteen days following vaccination. This case is offered as a confirmation of Leiner's theory.

TABLE I

No.	AGE	DATE OF AC- TION	FEVER	HEADACHE CONVULSIONS RIGIDITY OF NECK	LETHARGY UNCON- SCIOUSNESS	REFLEXES	EYE SYMPTOMS	PARALYTIC SYMPTOMS	DURATION OF INFESS	RESULT
1	7 1/2 yr	7	Yes	Headache	Lethargy			Immobility	19 days	Died
2		7				Increased	Photophobia	Spasticity of extremities	17 days	Died
3	6 yr	13		Headache Rigidity				Left hemiplegia		
4	17 mo	10	Yes	Convulsions				Spastic hemiplegia		
5	11 yr	12	Yes	Headache Vomiting				Cranial nerve palsies	14 days	Died
6	14 mo		Yes		Lethargy		Internal strabismus	Contracture of upper limbs		Recovered
7	13 mo	6						General muscular rigidity		Mental de-
8	5 yr	3	Yes	Headache Convulsions	Unconscious- ness	Absent	Upward rota- tion and fixa- tion	Spastic paralysis	4 days	ficency Died
9	5 yr	13	Yes	Headache Rigidity of neck	Lethargy		Ptosis right up- per lid	Spasm of left side of body	15 days	Died
10	2 yr	7	Yes		Unconscious- ness		Both eyes turned to right	Weakness of left leg		
11	12 yr	12			Lethargy	Anomalies			16 days	Recovered
12	21 mo	10			Unconscious- ness	Anomalies		Facial paralysis left side	28 days	Recovered
13	5 yr	2	No	Headache Rigidity of neck	Lethargy		Internal strabismus, ptosis of upper right lid	Spasm of extremities	26 days	Recovered

CLINICAL MANIFESTATIONS

According to Flexner,⁸ the two immediately arresting features of postvaccinal encephalitis are its hyperacute course and its high fatality. Prodromes including headache, vomiting, and pyrexia, plus paralysis, are regarded by the English as the cardinal symptoms of postvaccinal encephalitis.

According to Armstrong,² rigidity of the neck has been quite constant in American cases. The local vaccinal reaction has no peculiar character in the children who develop encephalitis.

Until recently it was believed that the occurrence of encephalitis after vaccination which locally had no result, i. e., a vaccination without a successful local 'take' could be excluded. However, the disease was described¹⁰ in a child aged thirteen years, which began five days after a revaccination and which was characterized by respiratory and nervous symptoms without any local reaction from the vaccination. After four days, the child died. Examination of the nervous system demonstrated lesions greatly resembling those found by others in cases of encephalitis postvaccinalis.

Recovery, when it takes place, tends to be complete. The outcome is independent of the stormy course and alarming character of the disease at the outset. Sequelae are very rare and are in striking contrast with the end results in cases of epidemic encephalitis of all grades of severity.

The clinical picture is not uniform. It may be that of tetanus, tuberculous meningitis, poliomyelitis or an obscure form of general intoxication not typical enough even to suggest encephalitis.

The recorded observations on 13 cases of postvaccinal encephalitis are presented in tabular form.

PATHOLOGY

The pathologic findings in the brain and cord establish postvaccinal encephalitis as a clinical entity. According to Flexner,⁸ even the gross appearance of the brain and cord in postvaccinal encephalitis differs from epidemic encephalitis. The lesions as disclosed by the microscope are more impressively distinct. The characteristic type of lesions in epidemic encephalitis is proliferative and infiltrative.

The findings in postvaccinal encephalitis consist of adventitial and periadventitial round-celled infiltrations distributed throughout the brain and cord. With appropriate staining methods, areas of myelin degeneration may be seen centered about the smaller vessels, which gradually fade into normal myelin structure. The characteristic softening or microglia proliferation about the blood vessels of the white substance of the central nervous system resembles the action of a toxic substance.

As compared with epidemic encephalitis, in which the lesions are nearly always confined to the brain, and chiefly to the basal gray matter, with much rarer involvement of the cortex and white matter, post-vaccinal encephalomyelitis is a disease in which both brain and spinal cord and both the gray and white matter of each, are implicated, and in which the white matter is attacked by preference. The brain and cord are diffusely affected, often without any particular choice of locality, though not everywhere with the same intensity. The lesions in the spinal cord are as important as those in the brain, if not more so.

It is a remarkable phenomenon that with lesions so widespread and severe in fatal cases, complete functional restoration takes place, as a general rule, in those that recover.

There are no characteristic blood and spinal fluid findings in this disease. German observers¹¹ found smallpox virus in the blood of 8 children between the third and tenth days after vaccination with reaction, and absent from the blood of 9 others. None of the spinal fluids obtained from the children contained virus, even when it could be demonstrated in the blood. The spinal fluid of one of the three infants with symptoms of postvaccinal encephalitis produced by the same vaccine, contained virus on the twelfth day after vaccination. The reports of other observers on the spinal fluid show essentially negative findings. The fluid is sterile, and at times, increased in pressure. There may, or may not, be a slight increase in the cell count. One case showed one hundred and seventy-nine cells per cubic millimeter. Tests for globulin were normal in some spinal fluids, while negative in others. Qualitative tests for sugar were positive in all the spinal fluids tested.

According to a Dutch authority,¹² the following points characterize postvaccinal encephalitis and differentiate it from epidemic encephalitis.

EPIDEMIC ENCEPHALITIS

1 Thick layers of lymphocytes and a certain kind of plasma cells in the perivascular lymph spaces.

2 Neuronophagia by glia cells, of which only a few were changed into granulated cells.

3 Preference for the gray substance.

4 Diffuse spreading.

5 Preference for the brain trunk.

POSTVACCINAL ENCEPHALITIS

1 Accumulations of microglial granulated cells outside the perivascular lymph space in the nervous tissue itself.

2 No neuronophagia.

3 Strong preference for the white substance.

4 Spreading in concentrated heaps.

5 Preference for the hemispheres.

PREVENTION

Considering the number of antismallpox vaccinations performed yearly, the chances for serious nervous system complications are infinitesimally small. However, the total number of such complications

is rather impressive, and may serve as a tool in the hands of various antivaccinationist elements. It may justifiably cause some concern to the regular medical practitioner.

While the problem of etiology is still unsolved, yet sufficient facts of epidemiologic nature have been accumulated to constitute a rational basis of prevention.

The important fact has been noticed that in countries where vaccination is practiced in infancy none, or very few cases of encephalitis, have developed. Also the number of cases of encephalitis following revaccinations is smaller than that following primary vaccinations. On the basis of these facts the English Committee recommends that primary vaccination shall be performed in infancy between the ages of two and six months and revaccination at the time the child enters school, five to seven years and again on leaving fourteen to sixteen years. In place of the officially advocated four insertions, trial shall be made of vaccination and revaccination in one insertion. Multiple scarification and cross hatching are deprecated. The Minister of Health is of the opinion that it is not generally expedient to press for the vaccination of persons of school and adolescent age who have not previously been vaccinated, unless they have been directly exposed to infection.

Sixty six per cent of all cases of postvaccinal encephalitis in England occurred between the ages of five and fourteen. Seventy nine per cent occurred in persons between the third fourth and fifth year of life. Infants under one year of age are relatively nonsusceptible to postvaccinal encephalitis.

In Holland, during the period covered by the report among 14 038 vaccinations from birth to one year 1 case occurred. Among 32 865 vaccinations between the ages of one and two years, 1 case occurred. In 1879 vaccinations between the ages of one and eleven years, 1 case occurred. This confirms the relative nonsusceptibility of young children.

In the countries where postvaccinal encephalitis occurred, it affected children mostly of school age, only rarely has a case occurred in infants under two years.

Knoepfelmacher states that not a single case of postvaccinal encephalitis has occurred among persons vaccinated by the intradermal method of Leiner. However it was impossible to ascertain the number of persons who were vaccinated by the intradermal method of Leiner on the basis of which the conclusion of Knoepfelmacher was made.

In connection with prevention of postvaccinal encephalitis, the work and views of Armstrong² merit the widest circulation and extensive clinical application. What follows is a condensation of the views of Armstrong.

Judicious exercise is essential for the fundamental well-being of familiar tissues, even to the bones and teeth. It may be assumed that the same is true of those tissues which constitute the defense mechanism, whatever and wherever they may be. Armstrong decided to determine whether preliminary immunization by the injection of non-specific antigens might increase temporarily an animal's efficiency in its reactions against a subsequent inoculation with vaccinia. This conception squares fully, or is identical with, the principle of non-specific protein theory. The parenteral administration of a non-specific antigen influences a subsequent infection. Similarly, an acute infection may favorably modify the course of a chronic infection. The "non-specific" stimulation of the defense mechanism constitutes the exercise for the defense mechanism which may be utilized therapeutically and prophylactically.

Armstrong attempted to verify experimentally the hypothesis that previous non-specific inoculations would render an animal's response to vaccinia more efficient. He made use of a strain of vaccine virus developed at the National Institute of Health, which was capable of producing a fatal meningo encephalitis when introduced into the brains of white mice. A dose of virus was selected through preliminary titration which was slightly less than sufficient to kill all of a group of normal mice. Preliminary to the intracranial inoculations with the most fatal vaccine virus, the mice were immunized against various antigens, diphtheria toxoid having been mainly used as the antigen. He then compared the number of deaths among previously immunized and nonimmunized groups following intracranial inoculation with vaccine virus. In each experiment, mice for the test and control groups were from the same shipment, and were placed under identical conditions.

The investigation showed that there were more survivals in the toxoid-immunized groups than in the other groups, and that the toxoid-treated mice tended to die later than the controls. The results indicated that the protection afforded by a previous non-specific stimulation is only relative, and not absolute. However, the test was a very severe one since the vaccine virus was injected into the brain tissue itself thus shunting out whatever mechanism there exists for protecting the central nervous system against vaccine introduced by other routes than into the central nervous system itself.

While the protection of a few mice from a cerebral virus infection by means of a previous non-specific stimulation of the defense mechanism does not necessarily lead to the conclusion that children could similarly be protected from postvaccinal encephalitis, yet the conception on which the work of Armstrong is based, and the limited amount of experimental laboratory evidence to support it, is sufficiently sound to accept its implications in practice.

Armstrong recommends that primary vaccinations, especially after the first year of life, be deferred until contemplated immunization against diphtheria or other diseases has been accomplished. The recent preliminary exercise of the immunity or defense forces may lead to a more efficient antiviral response with the result that the ensuing reaction may tend to simulate primary infant or secondary vaccinations in their comparative mildness and freedom from post vaccination reactions.

Since immunization against diphtheria is now almost universally practiced in this country it would be of value to put Armstrong's ideas and work to the widest clinical trial.

TREATMENT

In the absence of a definitely established cause of postvaccinal encephalitis, treatment must necessarily be empiric. Epidemiologic observations, however, furnish us with some facts on the basis of which certain broad prophylactic measures may be formulated. From the reports of the various commissions on this subject the following is adduced with regard to prophylaxis:

- 1 Postvaccinal encephalitis is much less frequent in young children than in older children.

- 2 No person should be vaccinated unless he is in perfect health.

- 3 Primary vaccination should be performed during the first year of life.

- 4 Secondary vaccination should be performed after ten years of age.

- 5 Attenuated vaccines should be used.

- 6 Only a single superficial skin insertion or puncture should be done with a minimum of trauma.

- 7 When a postvaccinal central nervous system complication follows it is infinitely less grave when it follows a vaccination made during the first months of life.

Therapeutically favorable results were reported from the use of blood serum from recently vaccinated persons. However the good results were not always uniform. Hekman¹³ had the opportunity to observe the therapeutic results of blood serum treatment simultaneously in two children aged two and four respectively. When the child aged two was admitted to the hospital seven days after being vaccinated with cowpox, it had spasms over the whole left side of the body. Both eyes were turned constantly to the right, also the head. During the attacks the face was pale and cyanotic. The child was unconscious, and the pulse was rapid—about 140. On the left upper arm were three distinct pox pustules with considerable reaction in the vicinity. The evening of the day of admission, the patient received

an intravenous injection of 10 c.c. of blood serum from the mother, who had been vaccinated at the same time as the child. The following day, the injection was repeated. The morning of that day the patient had still a few attacks, but toward noon they ceased. The child was, however, still unconscious, but the temperature began to fall, and in two days it had become normal. Twelve days later, the patient was dismissed as cured. The other child, aged four, received similar treatment but died, in spite of repeated injections of serum.

The British Report contains numerous observations on the efficacy of serum treatment. While serum treatment should be undertaken in every case, the exceptions are too numerous to regard it as a specific measure.

CASE REPORT

J. L., five years of age, third child. Full term, normal delivery. Birth weight, eight and one half pounds. Breast fed. History of whooping cough, measles, chickenpox, and occasional attacks of tonsillitis.

The child was vaccinated for smallpox on January 24, 1930. One or two days after vaccination, he began to complain of pain in his stomach and head, but he had no fever. Three days after vaccination, he began to vomit. There were no diarrhea, fever, chills, or cough. He lost weight rapidly, and gradually began to appear indifferent and drowsy. He complained of pain in the back only when moved.

The child was first seen Feb. 7, 1930, two weeks after vaccination. He was a well nourished boy, but somnolent, and answered questions slowly and with difficulty. Examination revealed a scrophoid abdomen, slightly positive bilateral Kernig signs, neck very rigid and painful on moving, generalized hyperesthesia of skin, internal strabismus and ptosis of right upper lid, pulse rate about seventy-five. Urinary findings were negative.

Lumbar Puncture. Eighteen cubic centimeters of clear fluid were withdrawn under considerable pressure. Cell count, one and one half hours after withdrawal, was 15 to 20 per c.m., consisting entirely of lymphocytes. Tests for globulin were positive. Qualitative test for sugar was positive. Ophthalmoscopic examination revealed normal eyegrounds.

Child gradually improved. Twenty-six days after the onset of symptoms, the child was well with the exception of slight ptosis of the upper right lid, which disappeared a few months later.

REFERENCES

1. Appendix III. Ministry of Health, Vaccination, Further Report of the Committee, London, 1930.
2. Armstrong, Charles. Postvaccination Encephalitis. Public Health Reports, July 22, 1932. U. S. Government Printing Office, Washington, D. C.
3. Gordon and Rhea. Post Vaccinal Encephalitis, *Am J Med Sc* 184: 104, 1932.
4. Roehm, Harold R. *Am J Dis Child* 44: 1293, 1932.
5. Reisch, O. *Wien klin Wchnschr* 43: 103, 1930.
6. Netter. *J A M A* 93: 578, 1929.
7. *Am J Dis Child* 44: 186, 1932.
8. Weichsel M. *Monatschr f Kinderheilk* 49: 28, 1931.
9. Flexner Simon. *J A M A* 94: 205, 1930.
10. Arie Querido. *Nederl Tijdschr v Geneesk* 75: 1047, 1930.
11. Ekstein A. Herzberg Krenmer, H., and Herzberg, K. *Deutsche med Wchnschr* 56: 264, 1930.
12. Bouman J. *Nederl Tijdschr v Geneesk* 71: 1980, 1927.
13. Hickman J. *Nederl Tijdschr v Geneesk* 73: 5227, 1929.

PHRENIC NERVE PARALYSIS IN THE NEWBORN, ASSOCIATED WITH DUCHENNE ERB'S PARALYSIS

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UNILATERAL paralysis of the diaphragm in the newborn has been but rarely reported, only nine such cases being found in the literature. Of these, seven alone were associated with simultaneous paralysis of the brachial plexus.

Weigert¹ in 1920 collected thirty cases of unilateral phrenic nerve paralysis from the literature, with one of his own, but only two of these were in newborn infants, and in no case was there verification by fluoroscopy.

It is not my purpose to discuss paralysis of the diaphragm in older children—due to tuberculosis, trauma, pressure on the phrenic nerve from various causes, diphtheria, or poliomyelitis—but to confine this study to the type of paralysis affecting the newborn. Accordingly I have brought together all reported cases tabulating and summarizing them for ready reference. To the cases reported two are added that have come under my personal observation.

The phrenic nerve, which is principally motor, has its origin mainly in the fourth cervical nerve, but receives additional fibers from the third and fifth cervical nerves, this last named association bringing it into the domain of the brachial plexus among the supraclavicular branches of which is one which communicates with the phrenic nerve. The nerve runs down the neck on the scalenus anterior muscle crossing this from without inward, and at the base of the neck accompanies it between the subclavian artery and vein. Entering the thorax it passes over the root of the internal mammary artery from within outward then follows an almost vertical course downward over the apex of the pleura and through the superior and middle mediastina to the upper surface of the diaphragm which it supplies with muscular branches. The right phrenic nerve is shorter than the left because of its more direct downward course and the greater elevation of the diaphragm on that side. Both nerves break up into terminal branches before reaching the thoracic surface of the diaphragm. Some of the branches of the right nerve, the phrenicoabdominal, traverse the diaphragm and pass to the muscle from the under surface.

From our knowledge of its anatomy, it is easy to understand how in a typical case of Duchenne Erb's paralysis the phrenic nerve may

¹From the Pediatric Department of the Brooklyn Jewish Hospital.

readily be damaged at the same time that the plexus has been injured at birth, whether the lesion be due to difficult or forceps delivery or to breech delivery

REPORT OF TWO CASES

CASE 1—Baby K, a boy, weighing 9 pounds 8 ounces at birth, which was by breech delivery, was seen at the office two weeks after delivery, June 21, 1928, suf



Fig 1 Case 1

fering with a cough and dyspnea. Physical examination revealed a large, well nourished infant, with a Duchenne Erb's paralysis on the right side, together with a hematoma of the sternocleidomastoid muscle. No cyanosis was present. The respiration was rapid, and there was slight dullness at the base of the right lung, with diminished breathing. No rales were heard.

On fluoroscopic examination the heart was seen to be pushed somewhat over to the left side. The diaphragm on the right side appeared high and exhibited the characteristic "paradoxical movement" first observed and named by Kienbock in 1895 in a case of pyopneumothorax. The right half of the diaphragm moved

up with inspiration, contrary to what occurs in normal respiration, while the left half moved down in the usual way thus showing a typical see-saw action, since known as *Kiesbom's phenomenon*. Roentgenograms of the chest at this time revealed that the right diaphragm was markedly raised being at least two intercostal spaces higher than the left and that the abdominal viscera were raised proportionately with it, while the heart was slightly displaced to the left. There was no evidence of diaphragmatic hernia. Repeated fluoroscopic examinations showed that within one month the diaphragm had receded to its proper place. One year later roentgen examination revealed a completely normal relationship between the right and left sides of the diaphragm. The child has subsequently developed normally in every way and the Erb's palsy has entirely cleared up.

CASE 2.—Baby L. M., a case of high forceps delivery, with weight 7 pounds 2 ounces at birth, was brought to the office two weeks later with a history of cyanosis. The essential physical findings were as follows: Right-sided Duchenne-Erb's paralysis, slight cyanosis, rapid respiration, dullness and diminished respiration at the right base, no râles. Fluoroscopic examination revealed that the diaphragm on the right side was at least two intercostal spaces higher than on the left with the characteristic see-saw action of the diaphragm. Roentgenograms confirmed these findings. One month later under fluoroscopy the diaphragm was seen in its normal position. Repeated examinations at subsequent dates showed a complete recovery from the right-sided Erb's palsy and the right phrenic nerve paralysis.

REVIEW OF THE LITERATURE

For convenience in summarizing the cases found in the literature, I have taken as a basis the tabulation drawn up by de Bruin,² making the necessary additions to include four more recent cases, and omitting the cases of Weigert¹ (1920) and Dyson³ (1927) which do not properly belong here, since in neither of these was there an associated paralysis of the plexus. Incidentally, however, these two cases refute Epstein's⁴ assertion that injury to the phrenic nerve without concurrent involvement of the brachial plexus has never been cited in the literature, and that one cannot conceive of such a phenomenon. Dyson's³ case was accounted for by the fact that in cutting through the umbilical cord which was wound several times around the neck the latter was accidentally incised with direct injury to the phrenic nerve resulting in paralysis of the diaphragm without an associated Erb's paralysis. Why in Weigert's¹ case the nerve alone should have suffered without the plexus sharing in the paralysis has not been explained.

A glance at our table shows at once that in every case the twofold paralysis followed a difficult labor or one with some abnormal feature. Thus in four cases there was forceps delivery and in five cases breech delivery, suggesting beyond a doubt that the condition was the result of a trauma inflicted at the time of birth. It is worthy of note that the injury was located on the right side in seven of the nine cases—an observation which is of importance for differentiation from *relaxatio diaphragmatica*, which may also exist in the newborn. In all nine cases the diagnosis was confirmed by the roentgen rays.

It was Kofferath,⁵ in 1921, who first reported a case of phrenic nerve paralysis in the newborn associated with Duchenne-Erb's paralysis of the brachial plexus.

TABLE I

	SEX AGE	DATE OF BIRTH	CLINICAL SYMPTOMS	ROENTGEN FINDINGS	RESULT	REMARKS
Kaffert (1921)	R	17 yr premature Low forceps Episiotomy	Distress immediately following birth. Dilated alae nasi, thoracic type of breathing	High position of diaphragm on right side, paradoxical move- ments. Heart pushed to left and downward upon inspira- tion	Cured after 4 months. Cessa- tion of paradoxical move- ments. Diaphragm still a little too high on right side	+
Landsberger (1920)	R	Breech presenta- tion Forceps Smellie	Asphyxia, cyanosis, peculiar short respiration. Diagnosis pneumonia. Symptoms ap- pearing soon after birth	High position of diaphragm on right side. Right half of di- aphragm moderately mov- able	Death from pneumonia 2 months after birth*	+
Friedmann and Chamber- lain (1927)	R	Low forceps	Attacks of cyanosis. Rales. Diagnosis pneumonia. First symptoms appeared after 14 days.	Paradoxical movements. Dia- aphragm high on right side	Plexus paralysis, cured in 14 days. Paralysis of dia- aphragm. Cured after 8 months, confirmed by roent- genogram	+
Eppstein (1927)	R	Breech presenta- tion Difficult labor	Rapid, irregular respiration im- mediately after birth. Right half of chest moved less than left half. Dullness and weak respiration. No rales	Right half of diaphragm high or by 4 ribs than left. Para- doxical movements. Entire right lung in shadow	Under observation until third year, 3 attacks of broncho- pneumonia. Roentgenologic changes persisted	+

* Autopsy. Diaphragm atrophic on right side. Fewer muscle fibers
or spinal cord atrophy and degenerative changes in phrenic nerve brachial plexus

TABLE I—Cont'd

	L OR R	BIRTH	CLINICAL SYMPTOMS	ROENTGEN FINDINGS	RESULT	PLEXUS PARALYSIS
Mulzer (1928)	L	Forceps. Long tedious birth.	In this mild case no clinical symptoms.	Movements normal on right side less movement on left. High position of diaphragm on left.	Rapid cure of N phrenicus and plexus	+
Remé (1930)	L	Primipara. Breech delivery difficult labor	Rapid breathing cyanosis immediately after birth. Abdomen contracted on inspiration. Became cyanotic upon crying.	High position of diaphragm on left side. Paradoxical movements.	Regression of plexus paralysis persistence of phrenic nerve paralysis at age of 1 year	+
de Bruin (1931)	R.	Second of a pair of twins. Breech presentation.	Pneumonia and pleurisy. Rales. Dyspnea.	High position of diaphragm on right side. Heart displaced toward left and downward.	Little change during 8 weeks of observation. Sudden death at age of 4 months. Cause unknown.	+
Stein (1933)	R.	Breech delivery	Rapid respiration. Dullness at base. Hematoma of sternocleidomastoid muscle.	High position of diaphragm on right side. Paradoxical movements.	Diaphragm had resumed proper place in 1 month.	+
Stein (1933)	R.	High forceps delivery	Cyanosis, rapid respiration, dullness and diminished breathing at right base.	High position of diaphragm on right. Paradoxical movements.	Diaphragm in normal position after 1 month.	+

This author sought vainly in the literature for another case of the same kind. He had noted soon after the birth of the child that respiration was unaccountably labored, and this observation, combined with evidence of injury from forceps at Erb's point, suggested to him that the infant was suffering with traumatic paralysis of the phrenic nerve. It was not until twenty-four hours later that the paralysis of the plexus also became evident, through a palsy of the right arm. The fluoroscope confirmed the injury to the phrenic nerve by revealing the classic paradoxical movement of the diaphragm. By the fourth day the paralysis of the nerve had passed, and respiration was normal. The plexus paralysis, however, slower to yield, did not disappear until the end of four months.

Two of the nine cases listed in the table terminated fatally. In that of Landsberger's in which the infant was delivered in breech presentation, pneumonia supervened soon after birth, to which the infant succumbed at the age of two months. At postmortem the diaphragm was found to be atrophic on the right side, and on microscopic examination it was seen to contain fewer muscle fibers than on the left side. This last finding furnishes definite proof that the case was not one of *relaxatio diaphragmatica*, which may equally be congenital and may present the same high diaphragm on the fallen side. A study of the phrenic nerve, brachial plexus and spinal cord revealed no changes either gross or microscopic in any of these structures.

In de Bruin's case the infant, who was the second of twins, born in breech delivery, was brought to the clinic at the age of four weeks, with a history of coughing and persistent refusal to take nourishment. A swelling of the sternocleidomastoid and the presence of a Duchenne-Erb's paralysis, both on the right side, together with the fact of a good general condition in other respects, suggested a congenital malformation, until the fluoroscope demonstrated a wide difference in the position of the diaphragm on the two sides with a definite *Kienbock's phenomenon* and a pushing of the heart toward the left side and downward. The case was under observation for six weeks, and gradual improvement noted, when at the age of four months death suddenly occurred, the cause of which remains unknown since it was impossible to obtain an autopsy.

The predominant clinical symptoms of paralysis of the phrenic nerve are cyanosis, dyspnea and other respiratory disturbances, together with disorders of nutrition in less degree. Thus in all cases but one (Mulzer's) the presence of pulmonary symptoms of one or another nature was recorded. In Epstein's case the child, under observation until the third year, suffered three attacks of bronchopneumonia and the roentgenograms showed the lesions still persisting. The low forceps case of Friedmann and Chamberlain likewise exhibited symptoms of pneumonia, but these did not appear until the plexus paralysis had been practically overcome, at the end of two weeks. Here the paralysis of the phrenic nerve persisted up to the eighth month, as was confirmed by roentgenogram.

Mulzer's case, one of the two left-sided ones, was rather exceptional in that the phrenic lesion was entirely symptomless and might have gone undiscovered in the presence of an Erb's paralysis had not roentgenologic examination brought to light the high position of the diaphragm on the left side.

The case of Remé, one of breech delivery, exhibited rapid breathing, cyanosis on crying and nutritional disturbances, which, according to that author, are of more importance when the lesion is on the left side. The fact of an Erb's paralysis of the left arm led to roentgen examination which revealed the presence of a high diaphragm on the left side and the characteristic *Kienbock phenomenon*. In this child at the age of three months, the chest was asymmetrical, with the left side more strongly arched than the right. The intercostal spaces were wider, and the ribs

took a more horizontal direction than those on the right side. When reexamined at the age of nine months the paradoxical movement of the diaphragm and its high position on the left side were still persisting.

COMMENT

The clinical picture has been well described by Hitzelburger¹⁰ in his special studies on the diaphragm. The great danger to which the patient is exposed if the paralyzed nerve does not quickly recover is that of pneumonia. The appearance of cyanosis and dyspnea shortly after an instrumental or difficult birth should lead the physician to suspect injury of the phrenic nerve. If such is the case physical examination will as a rule reveal soon after birth extensive changes similar to those observed in massive pneumonia or pleurisy but with normal temperature and a good general condition. Fluoroscopy will then disclose a high position of the diaphragm on the affected side and a typical paradoxical movement of the diaphragm (Kuenboek phenomenon) in breathing the affected side ascending during inspiration while the normal side descends, and the reverse of this in expiration like the see saw appearance of a pair of scales in perfect synchronism. The respiration is irregular and rapid and often there may be severe crises of air hunger. The type of breathing, unlike that of normal newborn infants is thoracic. In Epstein's case, the affected half of the chest made wider excursions in breathing than the healthy side. The heart is pushed out of place toward the affected side and downward.

SUMMARY

1 The rarity of the cases reported arouses the question whether paralysis of the phrenic nerve is not more common in cases of Erb's palsy than has been supposed. The complete absence of symptoms in one of the cases reported confirms such a suspicion. Attempts to check up this phase of the subject have been unsuccessful a number of newborn infants having been studied fluoroscopically for possible phrenic nerve injury but no cases being observed.

2 A study of nine cases of phrenic nerve paralysis associated with Erb's paralysis discloses that the great majority of cases are on the right side.

3 The prognosis is favorable as regards restoration of function in the very early days of life but appears to be less so if treatment is delayed two to three months. Even then the prognosis as to life is not unfavorable as shown by the cases of Reme and Epstein.

4 Paralysis of the phrenic nerve should be looked for in all cases of Erb's paralysis.

5 The suggestion is made that in view of Kofferrath having been the first to describe the syndrome of Erb's paralysis with phrenic nerve paralysis the name 'Kofferrath syndrome' be given to the condition.

REFERENCES

- 1 Weigert, R Bruns' Beitr z klin Chir 119 100, 1920
- 2 de Bruin, M Ztschr f Kinderh 51 45, 1931
- 3 Dyson, J E J A M A 88 94, 1927
- 4 Fpstein, J W Am J Dis Child 34 634 1927
- 5 Kofferath, W Monatsschr f Geb u Gynak 55 33, 1921
- 6 Landsberger Klin Wchnschr 5 850, 1926
- 7 Mulzer, A München med Wchnschr 75 1498, 1928
- 8 Friedmann, E, and Chamberlain, R S J A M A 86 934, 1926
- 9 Remé, G Arch f Kinderh 92 62, 1930 31
- 10 Hitzzenberger, K Das Zwerchfell im gesunden und kranken Zustand, Vienna
J Springer, 1927

135 EASTERN PARKWAY

MYELOSARCOMATOSIS

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THE diversity of opinions as to the etiology and character of leucemia is fully recognized. Briefly there are two schools of thought those who believe in the infectious origin of leucemia and those who consider the disease a true blastomatous process. In favor of the former are the acute leuceemias with abrupt onset septic course and short duration. In favor of the latter are the chronic leuceemias with insidious onset progressively downward clinical course and cellular infiltrations in the internal organs (Schultz¹). To strengthen the view as to the neoplastic character of certain cases of leucemia are those rare instances of complicated leucemia such as chloroma and leucosarcomatosis in which the accumulation of leucocytes assumes the form and character of tumor. Recently I have observed clinically and at autopsy an obscure form of disease and have attempted to classify it. I believe this case falls into the group of complicated leucemia and appears to substantiate the blastomatous nature of certain forms of leucemia.

CASE REPORT

History—A 8, a white boy aged six and a half years, was admitted to Sarah Morris Hospital on March 21, 1931 with the complaints of swollen eyelids and sinus trouble of one week's duration and pain in the stomach of two weeks duration. He was apparently well until December 1930 when he developed a cold and sore throat. One week later he complained of drawing pains in the wrists, elbows and anterior surface of the legs. The following day he experienced pain in the pit of the stomach worse during the night and unaccompanied by nausea or vomiting. This pain disappeared spontaneously in twenty-four hours. Three weeks before admission to the hospital he contracted chickenpox during which time the bone pains disappeared. During convalescence from the chickenpox the bone pains and epigastric distress returned and persisted off and on up to the time of hospitalization. One week before admission his mother noticed swelling of his right upper eyelid. The following day the left side of his face was immovable and the left upper lid swollen.

The child's past history included measles at two years and frequent sore throats for which his tonsils and adenoids had been removed at the age of four years.

His grandmother (paternal) died of carcinoma.

Examination—Examination revealed a well-developed but poorly nourished extremely pale and emaciated child. His temperature was 100.4 R. Blood pressure was 108/70 pulse 130 and respirations 36. Scattered throughout his scalp were many round pea to marble sized reddish purple nodules, firm in consistency and

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apparently attached to the underlying skull. They were most numerous over the parietal and frontal regions. He exhibited a left sided peripheral facial paresthesia. At the middle of the lower margin of the right mandible a small rough bony elevation was felt. The eyes were prominent but did not protrude. Both upper lids were brownish pink, swollen and indurated but nonfluctuant. His lips were dry and his tongue was coated. The tonsillar fossae and pharynx were slightly injected. The anterior and posterior cervical lymph nodes were slightly enlarged, more on the left, and were discrete and firm. The heart and lungs were normal. The abdomen was scaphoid and the spleen was palpated just below the left costal margin. No other organs or masses were palpated. The genitalia were normal. Except for marked emaciation the extremities exhibited no abnormal findings. The axillary, epitrochlear, and inguinal lymph nodes were not palpated. There were no pathologic reflexes.

Laboratory Data—

TABLE I
BLOOD FINDINGS

DATE	RBC	HB	WBC	POY- MORPH	LYMPHO- CYTES*	MONO- CYTES	EOSIN- OPHILS	BASO- PHILS	IM- MATURE RBC
3/25	3.0	75	6200	44	48	6	2	0	0
4/8	2.75	75	8000	45	48	6	2	2	3
4/13	—	—	7000	23	68	3	1	2	1
4/18	2.86	75	12,200	45	49	0	2	1	0
4/22	—	—	10,000	48	46	6	0	0	2
4/5	2.67	50	12,500	50	11	8	1	0	4

*Many of the cells classified as lymphocytes were large. The nuclei were purplish in color, the chromatin rather dense but not clumped as in the mature lymphocyte. Nucleoli were present and the nucleolar membrane was distinct. The cells contained abundant nongranular sky blue cytoplasm in which azurophilic granules were common (Wright and Giemsa stains). These cells might possibly be classified as lymphoblasts (Papainchin).

Chemical examination of the blood revealed normal nonprotein nitrogen, sugar, and cholesterol contents. Blood cultures on two occasions showed no growth. The blood Wassermann, Kahn, and the tuberculin tests were negative. Except for occasional granular casts the urine examination was repeatedly negative. Tests for Bence-Jones protein were negative.

Biopsy of Tumor Nodule of the Skull, April 7—Microscopic examination revealed a new formation of cells extensively invading the bone and surrounding structures. The cells were small and round consisting of scanty acidophilic cytoplasm and round nuclei. The nuclei showed variation in chromatin content. Many mitotic figures were present. Marked vascularization of the tumor growth was present and many of the blood spaces were lined by tumor cells. Necrosis of the adjacent tissue was marked. The impression was that of a malignant tumor—lymphosarcoma, round celled sarcoma, or leucosarcoma.

Course—On March 31 x-ray examination revealed a peculiar mothling of the skull particularly in the parietal bones, giving the appearance of having been "drilled by fine shot" (Fig. 1). The lower third of both femurs appeared moth eaten (Fig. 2). There was also a similar rarefaction of the shaft of the fibula just below the head. Films of the entire pelvis and lower spine exhibited the same moth eaten appearance. Films of the right arm disclosed erosion of the shaft of the humerus at the upper part of the lower third and of the radius below the head (Fig. 3). On April 7 two nodules were removed from the skull for microscopic examination (see biopsy report). The nodules from the skull were reddish purple

in appearance, pea to marble sized firm in consistency and involved the skin and underlying tissue. Secondarily many of the nodules had undergone abscess formation. Two such abscesses, one from each eyelid, were incised. Gram positive cocci were found on stained smear. From April 17 to April 20 many more nodules appeared on the scalp and over the back. At this time small shothike axillary and



Fig. 1.—Roentgenogram of the skull showing the moth-eaten appearance, the thinning and erosion of the cortex.



Fig. 2.—Roentgenogram of the femur showing moth-eaten rarefaction in the distal portions.

inguinal glands were palpated. An x ray of the chest on April 20 revealed no pulmonary neoplasm. The ribs, scapulae and clavicles showed areas of rarefaction (Fig. 4). On April 27 left proptosis was present and the patient complained of pain in the left parietal region. On April 27 the patient received the first of several deep x ray treatments to the skull and the long bones showing rarefaction. On

May 12 the bony elevation on the right mandible was enlarged and several more irregular nodules were palpated in the left supraorbital and frontal regions. The temperature had risen to 102° F. and the patient had begun to cough. There was evidence of bronchopneumonia in the right lower lobe. On May 20 the patient expired in a state of extreme emaciation.

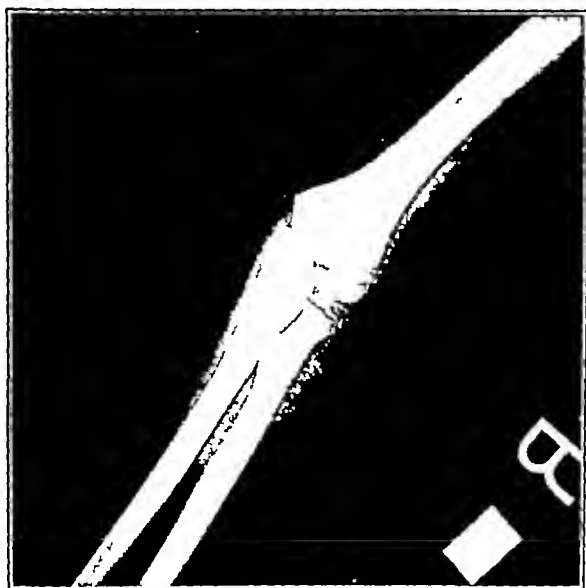


Fig. 3—Roentgenogram of the right arm showing erosion of the shaft of the humerus and the radius below the head.

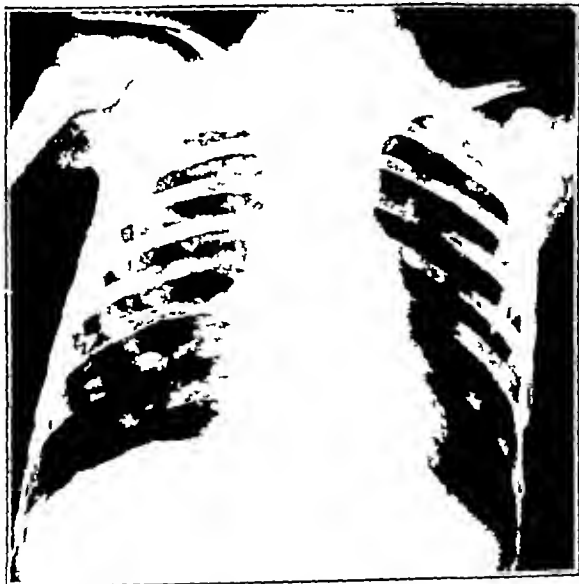


Fig. 4—Roentgenogram of the chest showing rarefaction in the ribs, scapulae, and clavicles.

AUTOPSY REPORT

Gross Findings—The autopsy was performed by Dr Otto Saphir pathologist, about four hours after death. The body was that of an underdeveloped markedly emaciated male child about six years old. The skin showed many small nodules measuring as large as 1 mm in diameter they contained a large amount of yellowish creamy material. Some of these nodules showed shallow ulcerations, a few of which were covered with a reddish brown crust. The skin was very thin and there was little subcutaneous fat tissue.

The serous cavities revealed no abnormalities.

The heart showed no gross changes.

Both lungs were air containing. The right lower lobe showed a few patches of bronchopneumonia.

The liver was larger than normal and of firm consistency. The capsule was smooth. On section the architecture of the cut surface in many portions was obscured. Where visible the central zones were red, depressed and some of them fused by confluence. The periportal spaces appeared bright yellow. No tumors or leukemic infiltrations were visible grossly.

The spleen was slightly larger than normal and of firm consistency. The cut surface was reddish brown. The trabeculae were clearly visible. The follicles appeared small and indistinct.

The kidneys were enlarged and soft. The capsules stripped away with ease leaving smooth surfaces. Throughout the surfaces, a few gray nodules were seen measuring up to 6 mm. in diameter. On section the architecture of the cortex was obscured. Nodules which were also visible on the cut surfaces appeared grayish and well defined. The pelvis, ureters and bladder revealed no gross abnormalities.

The pancreas and suprarenals revealed no gross changes.

The esophagus was dilated. The mucosa of the esophagus showed several small ulcers measuring 2 to 3 mm. in diameter which were surrounded by a yellowish necrotic tissue. Throughout the stomach, duodenum and jejunum many nodules were encountered which measured from 3 to 12 mm. in diameter. These nodules seemed to have risen in the submucosa and many were covered by mucosa with small areas of ulcerations. The nodules were very easily movable from the underlying muscularis; they were soft, light gray and revealed a homogeneous cut surface.

The lymph nodes throughout the body were slightly enlarged and softer than normal. On cut section they were gray and showed a finely granular surface.

The skull was much thinner than normal and showed many depressions and lacunations (moth-eaten). Between the calvarium and the dura a large, flat, yellowish brown tumor was noted, measuring 2 to 3 mm. in thickness. The tumor extended over the convexity of the brain completely filling the epidural space. It was firmly attached to the dura and could not be removed from the bone. The tumor did not extend into the arachnoid or brain. The base of the skull showed no tumor growth. Both orbits contained a large amount of edematous fat tissue but no tumor growth.

Multiple sections of the brain revealed no gross abnormalities.

The bone marrow of the sternum and ribs was grayish red. The bone marrow of the right tibia was light gray in some portions more yellow. It was much firmer and more compact than normal and showed a finely granular cut surface.

Histologic Examination—

Heart Sections of the myocardium showed no changes.

Lungs With the exception of a bronchopneumonia in the right lower lobe no abnormalities were noted.

Liver The liver cells showed a moderate granularity of the cytoplasm. The liver cells surrounding the central veins contained large fat globules. There was no cellular infiltration.

Spleen The follicles appeared atrophic. There was a slight increase of connective tissue throughout the pulp. The sinusoids were distended and filled with red blood cells. A moderate number of mononuclear cells were seen throughout the pulp. No accumulations of lymphocytes were found in any of the fields.

Kidneys The lining cells of the convoluted tubules were swollen, their cytoplasm was finely granular. In many portions the nuclei were absent. Some of the sections showed large accumulations of cells with paucity of cytoplasm, but distinctly outlined, deeply stained nuclei. These cells resembled large lymphocytes. They were found in several sections, but were situated mainly in the cortex (Fig 5). Giemsa stain revealed that only a few of these cells showed granules in their cytoplasm.



Fig 5.—Kidney. Section through kidney cortex showing infiltration of large mononuclear cells around glomeruli and proximal convoluted tubules. Many of the cells are round the nuclei dense and the cytoplasm sparse resembling large lymphocytes ($\times 120$).

Most of these granules were stained red, a few were blue. These areas of cellular infiltration corresponded with the nodules noted in the gross sections.

Suprarenals No abnormalities were noted.

Pancreas Throughout the pancreas very many cells, similar to those seen in the kidneys, were noted. They invaded the parenchyma in large masses, so that only outlines of pancreatic acini could be recognized. Giemsa stain showed very few granules in the cytoplasm of these cells.

Intestines Sections of the esophagus, stomach, and small intestines revealed, in the region of the submucosa, large accumulations of cells similar to those described in the kidneys and pancreas. In a few sections there was some necrosis which had led to the formation of small ulcers. Very few polymorphonuclear leucocytes were found in these regions. The sections which were taken from the esophagus showed many such ulcers. The blood vessels in these regions showed no changes.

Lymph nodes The architecture of the lymph nodes was preserved the sinusoids were distended. The follicles were small and indistinctly visible. Many large lymphocytic cells, poor in cytoplasm were found. Giemsa stain revealed no granules within the cytoplasm of these cells.

Skin nodules Sections which were taken from the skin nodules revealed mainly necrotic tissue, a moderate number of polymorphonuclear leucocytes, and a few large lymphocytic cells similar to those described before.

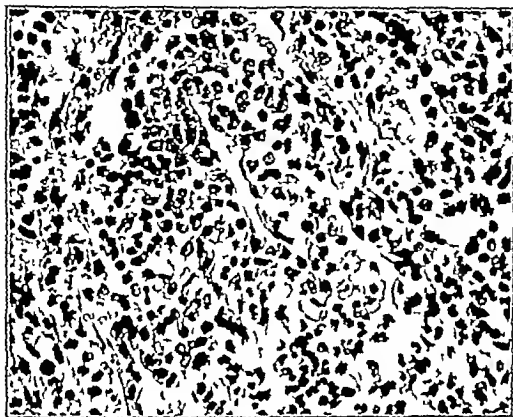


Fig. 6—Dura. Note the marked cellular infiltration. The cells resemble those in the kidneys. Variation in size, shape, and staining quality can be seen. There are a few mitotic figures. ($\times 250$)

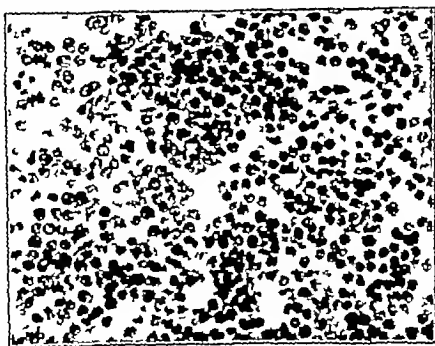


Fig. 7—Section of bone marrow showing the presence of large cells, many resembling macrocytes. There is variation in size, shape and staining quality. The normal marrow spaces are absent. Note the mitotic figures in the upper central field. ($\times 600$)

Dura Sections of the dura showed cells similar to those previously described (Fig 6) The nuclear details were not recognizable and very little cytoplasm was present Neither the Giemsa nor the oxydase stains revealed any granules There were no mitotic figures In only very few fields did the cells actually invade the deeper portions of the dura.

Brain Sections of the brain showed no abnormal changes

Bone marrow (tibia) In some of the fields the bone marrow showed cells similar to those described in the dura (Fig 7) The Giemsa and oxydase stains revealed a few granules within the cytoplasm Other sections revealed cells which were larger than those described before, which showed a loose chromatin network of the nuclei, and many mitotic figures The cells in general varied in size, shape, and staining quality, and appeared to infiltrate the bone marrow In many portions large areas of necrosis were seen in which only ghosts of cells were recognizable The Giemsa and oxydase stains revealed many neutrophilic, a few eosinophilic, and basophilic granules in the larger cells Some of the sections revealed an invasion of the bone and periosteum by these cells Sections which were taken from the bone marrow of the ribs and sternum showed a moderate number of fat cells in addition to occasional large cells similar to those described in the dura

DISCUSSION

The clinical and pathologic diagnosis in this case presented many difficulties The appearance of multiple tumors in the skull, proptosis, x-ray evidence of rarefaction and destruction in the membranous and long bones, marked anemia, severe emaciation and cachexia, suggested the possibility of generalized sarcomatosis (the primary focus unknown), chloroma, multiple myeloma, sympatheticoblastoma of the Hutchinson type, generalized xanthomatosis (Christian's syndrome), lymphosarcoma, atypical leucemia, and leucosarcomatosis Because this case offered so many diagnostic possibilities, and because the anatomic and histologic findings at autopsy were so unusual, it is felt that a detailed discussion of the differential diagnosis would be of value

Leucemia—Clinically I did not feel that this case was one of leucemia In infancy and childhood leucemia occurs most frequently in the acute form with a course resembling sepsis with extreme prostration and high fever, ulcerative and gangrenous lesions in the buccal mucosa, tonsils or pharynx, associated with enlargement of the lymph nodes and spleen, purpuric manifestations, and the presence of many immature lymphoid or myeloid cells in the peripheral blood Repeated examinations of the blood in this case failed to reveal many immature cells The superficial lymph nodes and the spleen were only slightly enlarged Diffuse destruction of bone as was found on x-ray examination is very unusual in leucemia Ewing² states that "the spongy trabeculae are often absorbed and even the shafts may be thinned, but a distinctly aggressive destruction of bone as in true tumors is missing" Postmortem findings were not typical of leucemia The lymph nodes did not show marked hyperplasia, the splenic follicles were atrophic, and the bone marrow consisted mainly of cells that

varied in size, shape, and staining quality, many of which revealed mitotic figures, rarely seen in leucemia,² but common in neoplasms

Chloroma—This disease is essentially one of early childhood, and is characterized by the development of infiltrating tumor masses in the cranial bones, orbits, paranasal sinuses, ribs, and sternum. Painful exophthalmos, progressive blindness, and deafness commonly occur. The sclera frequently have a peculiar greenish hue, unlike icterus. The lymph nodes, liver, and spleen are frequently enlarged. The presence of tumor masses in the alimentary tract may produce severe intestinal symptoms. The blood shows immature cells, either of the lymphoid or myeloid type usually with a moderate to marked leucocytosis. At autopsy tumor masses are found most commonly involving the periosteum, the dura, and the ligamentous structures. The tumor growths in a vast majority of cases are characteristically of *greenish color*. The bone marrow is red or grayish red, occasionally greenish. Histologically, the tumor cells tend to form parallel rows, and appear as large undifferentiated nongranular mononuclear cells. My case was not typical of chloroma. From the blood findings one could not establish the presence of leucemia, a great many of the bone marrow cells exhibited malignant changes conforming to a true neoplasm. The morphologic appearance of the epidural tumor, however, easily could have suggested the diagnosis of chloroma even though it did not present the characteristic green color.

Multiple Myeloma—Multiple myeloma is an exceedingly rare disease in childhood.⁴ It is characterized by a diffuse involvement of the osseous system with predilection for the vertebra, sternum, ribs, clavicles, scapula, and ilium. Paraplegia occurs in 40 per cent of the cases, indicating extensive disease of the vertebra. A pathologic fracture is frequently the first indication of bone disease occurring in 62 per cent of the cases and most commonly involving a rib.⁵ Marked involvement of the skull may produce exophthalmos and symptoms of increased intracranial pressure. Bence-Jones proteinuria is found in nearly 50 per cent of the cases. Berkheiser⁴ states that any marked change in the blood picture speaks against myeloma. X-ray examination reveals multiple areas of medullary rarefaction with erosion of the cortex, in places presenting a definitely punched-out appearance. Perforation is frequently observed. Histologically, the tumors are composed of large cells often resembling plasma cells lying in a vascular, delicate connective tissue and stroma. Clinically, I feel that it is possible to exclude multiple myeloma. Several examinations failed to reveal Bence-Jones protein in the urine. There were no pathologic fractures and x-ray examination in my case revealed a diffuse reddening of the bones involved unlike multiple myeloma in which the areas of rarefaction are usually isolated and sharply defined. The

epidural tumors and cellular infiltrations in the pancreas and kidneys found at autopsy are unusual in myeloma. Histologically, the tumor cells do not resemble the large plasma cell type usually found in myeloma.

Sympatricoblastoma—Sympatricoblastoma of the Hutchinson type is characterized in the majority of cases by swelling of the bones of the skull, exophthalmos, unilateral or bilateral with ecchymotic discoloration of the lids, profound secondary anemia without leucocytosis and the presence of an abdominal tumor in 50 per cent of the cases. Increased intracranial pressure with progressive blindness is common. The tumors in the cranial bones increase rapidly in size filling up the temporal fossae, and proptosis becomes so marked that the cornea ulcerates. The superficial lymph nodes are moderately enlarged. X-ray examination reveals a diffuse mottling of the skull, periosteal thickening of the long bones, and small areas of destruction. At autopsy a primary tumor is found, usually in an adrenal gland. Histologically, the tumor is composed of cells and their processes, derived from embryonic sympathetic nervous tissue. An abdominal tumor was not palpated in my case. Postmortem examination obviously revealed that we were not dealing with a sympatricoblastoma.

Lymphosarcoma—Lymphosarcoma occurs with greatest frequency between the ages of twenty and twenty-five years, and rarely in childhood.² It arises in the retroperitoneal, mesenteric, mediastinal, cervical, and superficial lymph nodes, and uncommonly in isolated nodes in the intestinal wall. Kundrat⁶ states that it is a regional disease of lymphoid tissue which spreads as a continuous growth through the lymph channels, thereby differing from the systemic character of leukemia. Isolated metastases in distant organs are rare, but in advanced cases the growth may invade the blood vessels, and true metastatic tumors form in the lungs, kidneys, skin, and other organs. In such instances atypical cells similar to those found in the tumor may also appear in the peripheral blood in large numbers, making the distinction between lymphosarcoma and leukemia difficult. A primary growth in the lymph nodes or lymphadenoid tissue could not be demonstrated in my case, the invasive and locally destructive characters of lymphosarcoma were absent in the organs involved, infiltration and accumulations of abnormal cells being the distinctive features. Also, anaplasia and mitosis of the cells were conspicuously absent in the lymph nodes described.

Xanthomatosis (Christian's syndrome)—In 1919 Christian⁷ described a clinical syndrome in children consisting of "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus." He considered a disturbed pituitary function as the cause of the syndrome. Rowland⁸ in 1928 associated Christian's syndrome with generalized xanthomato-

sia, a disease primarily the result of disordered fat metabolism in which the reticulo-endothelial system shows an excessive storage of lipoids, frequently in the form of cholesterol. The disturbed pituitary function is due to the encroachment of pseudotumors upon the pituitary body or tuber cinereum. Orbital involvement frequently causes exophthalmos. The most outstanding clinical feature is the presence of defects in the skull characteristically involving the inner table of the skull more than the outer, having distinct, clear-cut but irregular edges and often presenting a maplike or geographical appearance (Schüller). There is a tendency of the disease to spontaneous remissions and healing with new bone formation following x ray treatment to the affected areas.^{9 10 11} My patient showed no evidence of disturbed pituitary function; the course of the disease was progressive; x ray examination of the skull did not reveal distinct, clear-cut areas with irregular edges and x ray treatment of the affected regions did not result in healing. Two examinations of the blood revealed normal cholesterol values and postmortem histologic examination did not reveal the typical lipid laden xanthoma cells.

Leucosarcomatosis.—In 1904 Sternberg¹² attempted to isolate from recognized cases of leucemia certain cases characterized by the presence in the blood of large mononuclear cells which he believed to be pathologic lymphocytes arising from an original tumor and by means of true metastasis producing a generalized systemic disease. He applied the name leucosarcomatosis and called these cells "leucosarcoma cells." Anatomically this condition differed from typical leucemia in a more marked invasion into the lymphoid tissues particularly the mediastinum with tumor formations—a true blastomatous condition as opposed to a hyperplastic condition which he believed characteristic of the true leucemias. Within recent years the common belief is that the large mononuclear cells in the blood are myeloblasts or undifferentiated stem cells and that leucosarcomatosis is more closely related to myeloid than to lymphoid leucemia.

In 3 of Sternberg's original 6 cases a sarcomatous tumor was found in the mediastinum. Two cases exhibited tumor formation on the inner surface of the dura and in the skull. The spleen was enlarged in 5 cases and there was generalized enlargement of the lymph nodes in 2 cases. In 1915, eleven years later Sternberg¹³ reported a case of leucosarcomatosis which clinically resembles my case.

An eleven year-old child complained of fatigue and difficulty in breathing of five months' duration. Examination of the blood revealed a white blood count of 81,000 on admission and 5,250 shortly before death. Many large mononuclear cells "leucosarcoma cells" were observed at various times which led to the diagnosis of a probable leucosarcomatosis.

WBC 31,000 to 5,250, lymphocytes 4 to 28 per cent, polymorphonuclear leucocytes 5 to 30 per cent, myelocytes 4 to 9 per cent, "leucosarcoma cells" 42 to 85 per cent.

Postmortem examination revealed large, flat, firm tumors on the inner surface of the dura, enlargement of the spleen, liver, mediastinal mesenteric and retroperitoneal lymph nodes some of which were fused by confluence. The tumors of the dura consisted histologically, of large mononuclear cells similar to those found in the blood. The cells invaded the dura. Similar cells were found in large numbers in some of the lymph nodes and invaded the surrounding fat tissue. They were also present in the splenic pulp, in the interlobular spaces of the liver, and in the bone marrow.

It is true that some of the large mononuclear cells that were observed in the blood of my case and classified as lymphocytes, might possibly have been "leucosarcoma cells." Sternberg describes the tumor cells as being similar to those found in the blood. It is also possible that the abnormal cells in my case were identical with those found in the epidural tumor. In Sternberg's case the tumors showed a marked predilection for the lymph nodes and lymphatic tissues, mine was conspicuous for the paucity of lymphatic tissue invasion.

Realizing that it is at least not a clear case of leucosarcomatosis, a further search of the literature was made in an attempt to classify my case. This search revealed only one case, similar enough to warrant my using the classification presented therein.

In 1912, Buschke and Hirschfeld¹⁴ reported a case of a twenty-two year-old woman who, following a tuberculin injection, developed many tumor nodules throughout the skin. The blood picture was normal until four days before death when the white blood count rose from 11,000 to 33,000 and many peculiar "tumor cells" appeared in the blood. A puncture of the skin tumors revealed similar cells. The cells were large, the nuclei round, sometimes indented, and showed a dense chromatin network and often several nucleoli. The cytoplasm was stained sky-blue (Giemsa). In some of the cells azure granules could be found in varying numbers. A differential count at that time revealed polymorphonuclear leucocytes 35 per cent, small lymphocytes 23 per cent, large lymphocytes 8 per cent, large mononuclear cells 5 per cent, and "tumor cells" 25 per cent. Clinically, this was thought to be a form of leucemia consisting of abnormal cells classified by Pappenheim as "lymphoidocytes." The autopsy revealed in addition to a bilateral pulmonary tuberculosis, tumor nodules throughout the skin, some of which were the size of a walnut. The eyes were somewhat bulging, the lids swollen. The bones showed reddish gray tumor masses. The mucosa of the stomach presented tumor-like red excrescences. The large and small intestines showed ulcer-like depressions. Both ovaries and parametria were invaded by tumors. The lymph nodes surrounding the abdominal aorta were enlarged, firm, and infiltrated by tumors. When the scalp was removed, tumor nod-

ules could be demonstrated throughout the frontal region. The dura also was covered by firm tumor nodules throughout. Smears taken from the various organs revealed cells which were identified as lymphoidocytes. In the lymph nodes many mast cells were found. Many mitotic figures could be demonstrated. The skin tumors showed large mononuclear cells similar to those found in the blood.

In discussing their case Buschke and Hirschfeld state that there is no question that it is one of sarcomatosis. The primary tumor could not be located with certainty. They mention that in the literature there are cases of lymphosarcomatosis in which evidence of lymphatic leucemia is also present. They excluded this disease because they were unable to discover a new growth originating in the lymphatic organs. In their own case the tumors in the lymph nodes and spleen were relatively insignificant and were most marked in the bone marrow, skin, and ovaries, a pronounced deviation from the usual findings in lymphosarcoma. They considered as a second possibility leucosarcomatosis. The lymphoidocytes they described were not similar to Sternberg's "leucosarcoma cells", nevertheless, they were inclined to designate their case leucosarcomatosis in the sense that all leucemic proliferations, whether originating in myeloid or lymphatic hematopoietic organs, exhibiting a definite tendency toward an anatomically malignant growth of myeloid or lymphadenoid tissue should be called leucosarcomatosis. In summarizing their discussion they specify that theirs is the first case of leucosarcomatosis to be reported in which the new growth originated in the myeloid hematopoietic system and therefore proposed to classify it as one of 'myelosarcomatosis'. Several years later, Hirschfeld¹⁸ in discussing this same case states that the lymphoidocytes described were of myeloid origin and the skin tumors consisted of dedifferentiated myeloid tissue.

An analysis of my case brings out a striking similarity clinically and anatomically to Buschke and Hirschfeld's case of myelosarcomatosis. In both cases the white blood counts were only slightly elevated and the stained smears showed many atypical cells which resembled young lymphocytes. Hirschfeld is recently of the opinion that they are dedifferentiated myeloid cells. My case also exhibited nodules throughout the skin, many of which had undergone abscess formation, however, at autopsy many mononuclear cells were present resembling those found in sections of tumor nodules in other organs. Similarly, tumors were present in the bones, gastrointestinal tract and in the dura mater, consisting of cells many of which were myeloid in character. Both cases were conspicuous for slight lymphatic involvement. In many places the malignant nature of the growths was made evident by the presence of mitotic figures and invasion of surrounding structures.

SUMMARY

1 A case of an extremely rare disease in a child six and a half years old is presented in which the essential features are multiple malignant tumors throughout the skeletal system, gastrointestinal tract, kidneys, pancreas, and dura mater which histologically have the appearance of undifferentiated myeloid tissue. The blood revealed many atypical cells that resembled young lymphocytes but may have been myeloid in origin.

2 In an attempt to classify this case, a detailed clinical and pathologic differential diagnosis is presented.

3 Emphasis is placed upon the difficulty in separating certain cases of leukemia from neoplastic disease.

4 With a great deal of reservation I have classified this case myelosarcomatosis after Buschke and Hirschfeld.

104 SOUTH MICHIGAN AVENUE.

REFERENCES

- 1 Schultz, O. T. Tumors of Infancy and Childhood. Abt's Pediatrics, Philadelphia, 1926, W. B. Saunders Co., Vol. VIII, p. 830.
- 2 Ewing, James. Neoplastic Diseases, Philadelphia, 1928, W. B. Saunders Co., pp. 385-412.
- 3 Karsner, H. T. Human Pathology, Philadelphia, 1926, J. B. Lippincott, pp. 494-498.
- 4 Berkheiser, E. J. Arch. Surg. 8: 853, 1924.
- 5 Geschickter, Charles F., and Copeland, Murray M. Am. J. Cancer 16: 430, 1931.
- 6 Kundrat, A. E. Wien. klin. Wchnschr. 6: 211, 1893.
- 7 Christian, H. A. Defects in Membranous Bones, Exophthalmos, and Diabetes Insipidus. Contributions to Medical Research, New York, 1919, Paul B. Hoeber, Vol. I, p. 390.
- 8 Rowland, R. S. Arch. Int. Med. 42: 611, 1928.
- 9 Sosman, Merrill C. Am. J. Roentgenol. 23: 581, 1930.
- 10 Mettel, H. B. Am. J. Dis. Child. 42: 858, 1931.
- 11 Sparrow, Thomas D., and Fetner, L. M. J. A. M. A. 99: 2176, 1932.
- 12 Sternberg, C. Ztschr. f. Heilk. 25: 170, 1924.
- 13 Sternberg, C. Beitr. z. path. Anat. u. z. allg. Path. 61: 75, 1915.
- 14 Buschke, A., and Hirschfeld, H. Folia haemat. 12: 73, 1912.
- 15 Hirschfeld, H. Leukemie und verwandte Zustände. Schittenhelm, A. Die Krankheiten des Blutes und der Blutbildenden Organe, Berlin, 1925, Julius Springer, Vol. I, p. 472.

HYPERTROPHIC PYLORIC STENOSIS IN TWINS

ARTHUR F. VARDEN, M.D.
SAN BERNARDINO, CALIF.

LASCH¹ in discussing the etiology of hypertrophic pyloric stenosis suggested the study of its occurrence in twins as a likely means of determining, at least in some cases, whether this condition is congenital. He reported a case in one of monozygotic twin girls and from this concluded that it was probably not congenital. He suggested however, that a greater number of cases must be recorded before a definite opinion could be formed. One must be very cautious in concluding that this is not hereditary but environmental as monozygotic twins might be hereditarily different, due to an unusual splitting of the ovum giving rise to great variability in the anlage. This view is not generally accepted, however. Lasch's twins were physically identical and the placenta had but one corium. Single corium, while exceptional may also be found with dizygotic twinning though Lasch did not think the possibility of dizygotic twins applied to the case he reported. His patient died a few days after operation while the twin sister at no time showed symptoms or signs of pyloric stenosis.

Recent studies of mental disorders in twins by Rosanoff² should throw considerable light on the etiology of these conditions as regards heredity and environment. This method of clinical investigation also lends itself to the study of physical disorders and particularly pyloric stenosis as Lasch has pointed out.

The comparative rarity of this condition, together with the fact that obstetricians report that approximately one birth out of 80 is multiple makes the possible number of cases small. It is difficult to determine from some reports whether the twins are monozygotic or dizygotic. Wherever possible, this has been investigated by correspondence.

All the reported cases discoverable were reviewed with the hope that interest would be created in reporting diseases occurring in monozygotic and dizygotic twins. In time a sufficient number may be recorded to make some conclusions possible on this and other conditions.

Redalin mentioned pyloric stenosis in two sets of twins, but said nothing about the type of twinning so his cases cannot be used.

Davis,³ in 1924, reported pyloric stenosis in twin boys, but unfortunately the records do not show whether the twins were monozygotic or dizygotic (Personal communication). The diagnosis was confirmed by operation and both patients made uneventful recoveries.

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Moore's⁴ cases also occurred in monozygotic twin boys (Personal communication) They were not seen until the fourth week after onset, at which time their condition was precarious as well as complicated by malaria Both presented typical signs and symptoms of pyloric stenosis, diagnosis being confirmed at operation Due to their poor condition both died about a week after operation

Bilderback's⁵ twins were monozygotic (personal communication), two months premature males Typical tumors were found at operation One twin died while the other made an uneventful recovery

Moniadi⁶ reported 228 cases of hypertrophic pyloric stenosis of which three cases were in three pairs of twins The type of twinning was not mentioned but since they were normal one would suspect them to be dizygotic even though Lasch did not find it so in his cases

Because of the discussion as to identification of monozygotic twins, the following criteria were used to establish this in our cases

(1) Both were males, identical in every way by physical examination except one was more emaciated due to earlier onset of symptoms,

(2) Hand prints were taken and found sufficiently alike to be classified as "1 Absolute Ab 1" according to Reichle⁷

(3) For additional proof the obstetrician's note at time of delivery is quoted "The placenta was a large one in size although it was not weighed Each cord was inserted at opposite sides of the placenta, each one having a battledore attachment There was only one chorion present The amnion separated two amniotic sacs No line suggestive of a fusion of two placentas could be found It was apparently composed of only one placenta, and in every way appeared normal"

CASE REPORTS

CASE 1—*History*—T K, aged nine weeks, was admitted to the University of California Hospital, February 9, 1931, with the chief complaint of vomiting since one month of age Family history was significant as mother had arrested pulmonary tuberculosis and the twin brother had also been vomiting although not so much Delivery had been by low forceps, birth weight 6 pounds, with question of prematurity No breast milk was available and he was given whole cow's milk, boiled, diluted with water After a week this was changed to Dryco upon which he did well for three weeks then started vomiting Formula was again changed to lactic acid milk, next to diluted evaporated milk and later to Eagle Brand milk without improvement For one week before entry he was given atropine 1/1000 to 1/600 grain before feedings The vomiting continued, occurring shortly after feedings and at times was projectile For two days previous to admission the vomitus contained material resembling coffee grounds and he vomited water as well as milk Intramuscular blood (15 cc) was given Marked constipation had been noted for two weeks although enemas showed some return There had been no infection.

Weight on admission was 3170 grams and patient was markedly dehydrated, emaciated and pale having the typical appearance of a "little old man" with very thin cheeks and sunken fontanel He seemed very hungry and sucked his fists con-

stantly. Skin was pale, dry and inelastic and there were small shotty glands in the cervical and axillary regions. Chest was poorly clothed but otherwise negative. Abdomen was scaphoid, thin and a small firm tumor mass could be felt in the right upper quadrant. No peristaltic waves could be made out at any time.

Laboratory Data.—Blood on admission was Hemoglobin 82 per cent (Sahli) RBC. 6,110,000 WBC 18,500 Diff. Polys 52 Lymphocytes 45 Mononuclear 1 Basophiles 1, Myelocytes 1. Blood hematuria. Plasma CO = 64.3 volumes per cent, Plasma Cl = 470 mg per 100 c.c. N.N. = 2.3 mg per 100 c.c. Wassermann and Tuberculin 01 were both negative.

Barium meal with fluoroscope showed 80 per cent gastric retention at the end of 6 hours. Bronchopneumonia was revealed in the permanent films made



FIG. 1—T. R. left D. R. right. Aged twenty-one months.

Treatment.—Patient was given parenteral fluids and thickened feedings preceded by phenobarbital 0.004 gram. Projectile vomiting of water and formula continued and gastric lavage consistently showed marked retention of food in the stomach.

After further preparation with parenteral fluids a Rammstedt operation was done on February 10 1932. A typical pyloric tumor was found. Just before closing the abdomen the peritoneal cavity was filled with normal saline.

After operation, the infant retained the first few small feedings of whole lactic acid milk with added Karo sugar but then began to vomit. Vomitus contained old blood. His temperature was 38.6 C. He coughed occasionally but his chest was negative to physical examination. He continued to vomit most of his feedings and the amount of blood increased so that the second postoperative day he ap-

Moore's⁴ cases also occurred in monozygotic twin boys (Personal communication) They were not seen until the fourth week after onset, at which time their condition was precarious as well as complicated by malaria Both presented typical signs and symptoms of pyloric stenosis, diagnosis being confirmed at operation Due to their poor condition both died about a week after operation

Bilderback's⁵ twins were monozygotic (personal communication), two months premature males Typical tumors were found at operation One twin died while the other made an uneventful recovery

Monrad⁶ reported 228 cases of hypertrophic pyloric stenosis of which three cases were in three pairs of twins The type of twinning was not mentioned but since they were normal one would suspect them to be dizygotic even though Lasch did not find it so in his cases

Because of the discussion as to identification of monozygotic twins, the following criteria were used to establish this in our cases

(1) Both were males, identical in every way by physical examination except one was more emaciated due to earlier onset of symptoms,

(2) Hand prints were taken and found sufficiently alike to be classified as "1 Absolute Ab 1" according to Reichle⁷

(3) For additional proof the obstetrician's note at time of delivery is quoted "The placenta was a large one in size although it was not weighed Each cord was inserted at opposite sides of the placenta, each one having a battledore attachment There was only one chorion present The amnion separated two amniotic sacs No line suggestive of a fusion of two placentas could be found It was apparently composed of only one placenta, and in every way appeared normal"

CASE REPORTS

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blood and a markedly positive benzidine test for blood was also noted in the few stools passed. Gastric lavage twice daily consistently showed considerable retention. February 13, a Rummstedt operation was done under local anesthesia and a typical olive-shaped tumor was found. A small section taken for examination revealed hypertrophy, hyperplasia, interstitial edema and hyalinization of pyloric smooth muscle. Just before closure of the wound the abdomen was filled with normal saline. His postoperative course was uneventful. He took gradually increasing amounts of formula without vomiting and his weight steadily increased. His stools later became negative for blood. He was transfused to improve his anemia but as in the case of his brother this was difficult because of an apparent anomaly in the valves of his veins.

Patient was discharged 15 days after operation weighing 4380 grams, a gain of 190 grams since admission and continued to do well.

Both patients were seen again in September 1932, aged 21 months. They had been perfectly well since discharge. T. K. weighed 31 pounds 10 ounces and was 34½ inches tall, while D. K. a weight was 30 pounds 7 ounces and his height 34½ inches. T. K. has been five months behind his twin in development, that is, walking, talking, etc.

CONCLUSIONS

1 Hypertrophic pyloric stenosis is reported in monozygotic twin boys. A review of previous reports shows that accurate information regarding monozygotic or dizygotic twinning is seldom mentioned, decreasing the value of these reports. Reports of pyloric stenosis occurring in only one of twins should likewise be carefully reported regarding placentation.

2 Hypertrophic pyloric stenosis in twins is rare and in the small number collected one would conclude that there is more evidence in favor of a congenital theory than against it but one must await the recording of more cases before a real conclusion can be made.

REFERENCES

- 1 Laseh Von W. München med Wochenschr 72 1155, 1925
- 2 Rosanoff Arron J. Calif. and West Med 37 101 1932.
- 3 Davis, H. H. J. A. M. A 83 686 1924.
- 4 Moore, H. L. Southern M. J 17 187 1924
- 5 Bilderback J. B. Northwest Med. 27 182 1928
- 6 Monrad D. Monatschr f Kinderh 37 473 1924
- 7 Reichele Hubert S. Biological Bulletin 58 164 1929

peared very pale and decidedly worse. His hemoglobin was 34 per cent (S) R.B.C 1,780,000. He was given 75 cc citrated blood with great difficulty, presumably due to an anomaly of the valves in his veins. Following this transfusion he improved generally, vomited less but his stools became dark and tarry. His hemoglobin was 42 per cent (S) and R.B.C 2,480,000.

Two days later he was transfused again with the same difficulty. Parenteral fluids were administered as needed. After a third transfusion his hemoglobin went up to 65 per cent (S) and his R.B.C were 3,700,000.

After five days vomiting ceased and the small amounts he spit up did not contain blood although his stools continued to be tarry for a few days longer and a positive Benzidine test was obtained for a still longer period, but finally the stools became normal. He gained slowly and additional transfusions were necessary.

On April 6 he had fever and signs of bronchopneumonia were present, most marked on the right. This was confirmed by roentgenogram. The following day the left ear drum was incised and drained pus for a few days. His cough and a low grade fever persisted. Chest films remained unchanged and suggested perifocal tuberculosis. Tuberculin test 10 mg which was repeated, was negative.

Since his weight had become stationary the formula was changed to two parts evaporated milk to one part of stock solution, following which he gained steadily in spite of occasional vomiting.

On March 26 he developed definite signs of whooping cough after an accidental exposure some days before. He became extremely ill, cyanotic and toxic and vomited constantly. He was given pertussis vaccine without demonstrable improvement. He improved when placed in an oxygen tent but became cyanotic whenever removed for feedings. After a very stormy course he was discharged from the hospital on June 29, 1931, still having a slight cough but afebrile and otherwise in good condition. Discharge weight 5800 grams.

CASE 2—History—D K., white male, aged nine weeks, was admitted to the University of California Hospital on February 10, 1931, with the same complaint as his brother, who had been admitted the previous day, vomiting since one month of age only less severe. Birth and feeding history were practically the same as that of twin brother. He did well for a month when he began to vomit a small amount of formula. This usually occurred immediately after feeding, never longer than one half hour. Vomiting was projectile in type and did not show mucus, blood and bile. Vomiting continued intermittently for two weeks during which he lost most of his feedings, so the formula was changed to evaporated milk 6½ ounces, water 14 ounces, 4 ounces every four hours, with cessation of vomiting until two days before admission. During this final period he vomited practically everything including water. He had gained 3 ounces since birth but failed considerably during the past three weeks. Stools had been few and constipated and there had been no infection or fever.

Physical examination on admission revealed a well developed but poorly nourished dehydrated infant, weighing 3800 grams. His skin was inelastic, dry and pale. He had a soft scaphoid abdomen, and a definite small firm mass could be felt in the left upper quadrant but no peristaltic wave could be made out.

Laboratory Data—Hemoglobin 63.7 per cent (S), R.B.C 3,150,000, W.B.C 10,900, Polys 32 per cent. Tuberculin negative. Plasma CO₂ 43.7 volume per cent. Barium meal under fluoroscopy showed marked retention.

Treatment—For three days following admission whole lactic acid milk with 10 per cent added Karo thickened with rice flour, was given every four hours with phenobarbital 0.004 twenty minutes before each feeding. Additional fluids were administered parenterally. Vomiting continued and soon became dark red with

set far apart with their horizontal axes directed laterally and strabismus is often present. While the height and circumference are usually normal, the skull length is shortened and the occiput flat, giving a brachycephalic type.

Physical development may be normal or retarded. Mental deficiency may or may not be present and other deformities may be found, such as syndactylism, high palate, undescended testes, and acrocyanosis.

X ray of the skull shows the wide separation of the orbits and large anterior nares. Intersutural bones may be present or the sutures incomplete with absence of digitations.



Fig. 1—Case 1



Fig. 2—Case 2

According to Reilly, the most common form is that with facies and a family tendency, our cases falling into this variety.

We are describing briefly two cases, a female twelve years of age and a male of six years, brother and sister. The mother of these children, aged forty years, has the typical hypertelorism more marked than the daughter or son. She appeared very sensitive about her condition and would not consent to allow us a picture of herself, although she showed us a picture taken in her infancy which illustrates the facies quite well. On further question it was found that her father also had a similar appearance. As near as we could determine the mentality of both adults was apparently normal. A third child, the oldest in the family, is the only normal one.

CASE REPORTS

CASE 1—Ed D, male, six years of age, was brought to the physician because of frequent sore throat and head colds

The history of birth and development appeared entirely normal, and his general health was excellent

On casual inspection, attention was immediately drawn to the eyes which appeared to be wide spread, and the mother volunteered that the boy had been that way since birth and that her second child, a girl, had the same type of face

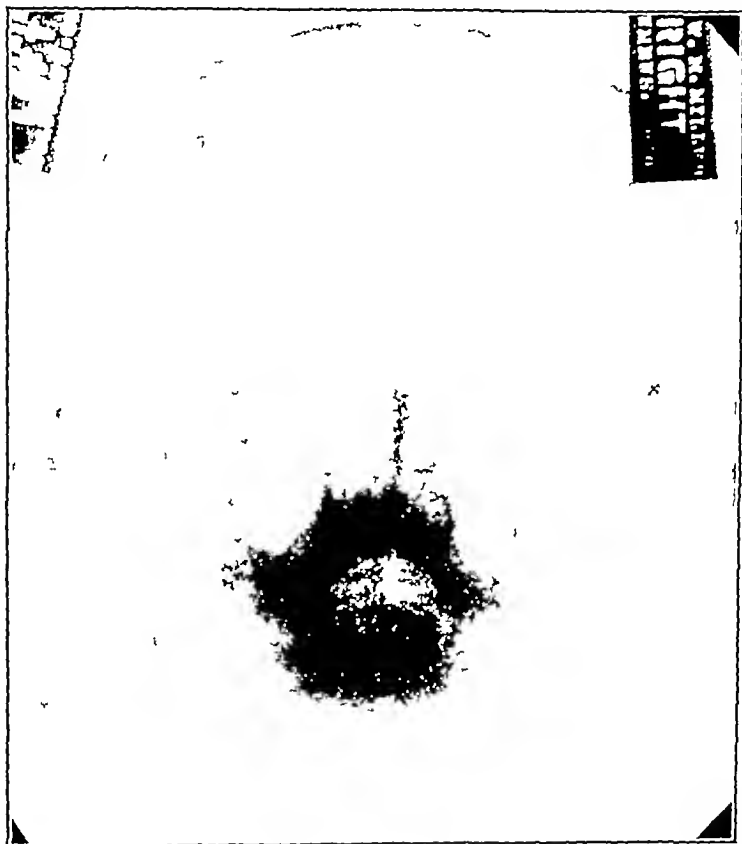


Fig 3—Case 2

The essential findings are in the face and head. The skull seemed unusually large, particularly in width, the occiput rather flat, the forehead high, while the frontal and orbital prominences were very slight. It would seem that the skull has been flattened from before backward.

The other notable feature was the appearance of the eyes, seemingly far apart. The bridge of the nose was moderately depressed and broad, the nose not being retroussé.

The eyegrounds were normal and no definite strabismus was noted. The hard palate seemed high and the child spoke with a mild defect in articulation.

Physically and mentally, the child appeared to be normal in all other respects. Tuberculin and Wassermann tests were both negative.

While this child is a mild case and the picture is not particularly convincing the facies was characteristic on actual inspection and served to discover the more definite case in the sister and also bring to light the definite familial history in the parent and grandparent. X ray of the skull was not unusual.

CASE 2.—Em D., a sister twelve years of age, presented a more definite facies than her brother.

Her birth developmental and past medical histories were all quite normal. She appeared unusually alert and intelligent and was quite sensitive about her face.

The eyes were unusually far apart. The bridge of the nose was greatly depressed and broadened while the nose was retrousse. The face seemed small in comparison to the cranium.

There were no other abnormal physical findings.

Table I gives measurements in millimeters of patients and comparison with normal subjects of the same ages.

TABLE I

ORBIT	EM D PATIENT	6 YR. NORMAL	EM D PATIENT	1 YR NORMAL
Between internal canthi	35 mm.	30 mm.	45 mm.	24 mm.
Between external canthi	105 mm.	85 mm.	105 mm.	90 mm.
Between center of pupils	60 mm.	—	60 mm.	—
Right orbital height	30 mm.	23 mm.	28 mm.	25 mm.
Left orbital height	30 mm.	22 mm.	28 mm.	25 mm.
Right orbital width	40 mm.	30 mm.	45 mm.	35 mm.
Left orbital width	40 mm.	30 mm.	45 mm.	35 mm.
SKULL				
Greatest circumference	415 mm.	500 mm.	543 mm.	525 mm.
Greatest length	170 mm.	170 mm.	170 mm.	170 mm.
Greatest width	140 mm.	130 mm.	160 mm.	140 mm.
Cephalic index	83.3 mm.	76 mm.	94.1 mm.	80 mm.

(The cephalic index is obtained by multiplying the cranial breadth by 100 and dividing by the cranial length.)

The following is the radiologic diagnosis of the x ray of Em D. (Dr W. H. Miller.)

Skull. X ray examination of the skull made in the lateral and anteroposterior views shows an overgrowth of the lesser wings of the sphenoids which have ossified early and grow excessively. The orbits are widely separated due to the overgrowth of the wings of the sphenoids. The anterior portion of the skull is irregular in outline. Suture lines are normal.

Teeth. Normal.

Sinuses. Normal.

Sella Turcica. Slightly enlarged.

SUMMARY

Two cases of hypertelorism with a definite familial history, all without mental deficiency are reported.

350 E. STATE STREET

REFERENCES

1. Williamson, Bruce. *Diseases of Children*. New York: Wm. Wood & Co., p. 12.
2. Garrod, Batton, Thurahfield and Paterson. *Diseases of Children*.
3. Grieg, D. M. *Edinburgh M. J.* 31: 560, 1924.
4. Reilly, W. A. *J. A. M. A.* 96: 1929-1931.

in the first few days. These began to disappear and by the time the temperature was normal he was symptom free, except for an occasional sweat. There was no change in his weight during his hospitalization. He was discharged symptom free after two weeks' stay in the hospital and at the end of three months is apparently well. The duration of symptoms was eleven weeks.

Epidemiologic Study—After the confirmatory evidence afforded by laboratory work, we attempted to investigate the milk supply. The milk was obtained from a special herd which gave no history of abortions. The milk was not pasteurized and the dairyman had forgotten to tell the mother to boil the milk, as was his custom when babies were started on this brand. The milk was not labeled as pasteurized. Blood studies in this herd revealed a number of positive and suspicious reactors.

SUMMARY

1 A case of *B abortus* infection, beginning in a seven-months old infant is reported.

2 This is the first case to our knowledge that has been reported from this section of the country in infancy or childhood.

3 A clinical diagnosis was made and was verified by positive blood culture and agglutination test.

4 *B abortus* infection in infancy may be more frequent than is now recognized. Any unexplained fever should suggest the possibility of its occurrence.

5 Universal use of pasteurized milk will eliminate this disease in the early years of life.

REFERENCES

- 1 Hubbard, J. P. J. PED 1 464, 1932
- 2 Hill, W. O., and Monger, R. H. J. A. M. A. 97 176, 1931
- 3 Dietrich, Henry, and Bouvage, Charles W. J. PED 1 46, 1932

ALLERGIC EPILEPSY

J KLEIN M D
CHICAGO ILLINOIS

IDIOPATHIC epilepsy is a clinical syndrome which is as yet not clearly understood. The observation of an asthmatic child suffering from epileptic seizures brought up the question of allergy in relation to epilepsy. Spangler¹ studied 100 consecutive cases of adult epilepsy and found that in 88 per cent there was a history of allergy in the ancestors. He notes that gastrointestinal allergy is an important factor in the development of convulsions in the epileptic child. In his series Spangler reported that 32 per cent of the patients had convulsions in infancy. Among the parents and grandparents he found 11 cases of epilepsy, 35 cases of asthma, 7 of hay fever, 14 with urticaria, 6 with a history of eczema, and 6 who had migraine. Multiple allergic manifestations were observed in one third of all the epileptic patients.

A. H. Rowe² states that allergy is undoubtedly the cause of certain cases of epilepsy especially in children. He reports two such cases: (1) a four year old asthmatic child who was sensitive to pollens and in whom immunization resulted in freedom from asthma and cure of the epilepsy, and (2) an eleven year-old child who suffered from petit mal for six years and was sensitive to cat hair, and rabbit hair. Desensitization to horse hair and removal of her hair mattress resulted in complete relief for two years. S. J. Levin³ reported a three-year-old child with epileptic seizures in association with sensitization to American, Swiss and Roquefort cheese. On eliminating cheese from the diet there was a complete cessation of epileptic reactions. Levin gives credit to Pagniez and Lientaud⁴ for having first pointed out the frequent occurrence of allergic manifestations in certain instances of epilepsy. Their first report was that of a young man who suffered from epileptic seizures which were induced by eating chocolate.

In this country J. L. Miller⁵ was among the first to emphasize the importance of allergy in relation to the epileptic syndrome. He expresses the opinion that the epileptic seizure is an anaphylactic manifestation, and thinks that in some cases of epilepsy food sensitization is responsible.

Angiospasm is an important factor in the explanation of epileptic manifestations and is regarded by some as one of the effects of allergy. There are a number of authorities who explain the epileptic syndrome on the basis of a cortical ischemia induced by angiospasm (Perez, Olkan, Bolsi, Etienne).

Back of these allergic and epileptic manifestations there is some hereditary defect which is transmitted by the germ plasma. Thus Frugoni⁶ has proved that the allergic constitution is transmissible through either parent, although the type of manifestations may differ in parent and child.

As to the nature of this metabolic or constitutional defect, little is definitely known. However, Auguste Lumiere⁷ in 1921 published a brilliant hypothesis in his study on the rôle of colloids in biology. This work deserves to receive more attention since it is based on experimental evidence and seems of great practical importance. Lumiere maintains that anaphylactic phenomena are due to an alteration in the colloids of the tissue fluids and blood plasma wherein the usually finely dispersed colloid particles are agglutinated and form precipitates in the perivascular lymphatics and tissue spaces. A flocculation of these altered colloid particles in the lungs causes asthmatic symptoms, in the brain it results in epilepsy. Lumiere went further and suggested that treatment should aim at dissolving or breaking up this abnormal state of the colloids. Lumiere's theories and experiments are deserving of more intensive investigation.

Because of its implications and clinical interest I wish to add the following clinical record to the literature.

L. B., aged eight years, first attended the Pediatric Department at Northwestern University on March 21, 1931. She complained of frequent attacks of dyspnea, which had been occurring at irregular intervals since the age of six months. She also coughed frequently, and was 10 per cent under weight. L. B. was the first born child and had been breast fed. As an infant she was very fat. At one month of age the patient developed eczema which persisted until she was two years old, and has never recurred. The periods of asthmatic dyspnea appear every few days and at times are so severe that she becomes cyanotic.

She had measles, whooping cough, hay fever, and later pneumonia complicated by empyema (aged six years). Tonsillectomy and adenoidectomy were performed at four years of age. The family history was not very illuminating. The mother had died of pneumonia and heart trouble at twenty-eight years of age. The father is living and well. No history of familial asthma, hay fever, hives, or epilepsy could be elicited from an aunt who accompanied the child.

On Jan. 28, 1930, the patient had an attack of epileptic convulsions. The attack was preceded by a severe paroxysm of asthma and followed by cyanosis and coma. Since then the patient has been troubled by epileptic convulsions, which occur every week, sometimes several times weekly. It was found that the number of attacks was reduced by the asthmatic treatment. When the latter was omitted for a period of four months, the epileptic seizures increased in frequency.

On physical examination the patient was found to be of asthenic habitus and very much undernourished. Her cheeks were flushed. The respirations were frequent and labored.

Examination of the head and neck showed no noteworthy defects. The eyes reacted to light and accommodation. The ears were normal, as was the hearing. The teeth were apparently normal. The tonsils had been removed. The tongue in its anterior half presented enlarged, congested papillae which gave it a "raspberry" appearance.

The thorax was barrel shaped and the sternum was unusually prominent. There was very little motion of the chest on respiration. The lungs were hyperresonant and emphysematous. The breath sounds were distant. Numerous fine and coarse piping râles were heard on expiration.

The heart borders were indistinct because of the emphysema. The apex was in the fifth interspace and in the mid clavicular line. The heart tones were muffled. There were no murmurs.

The abdomen was retracted. No localized rigidity or tenderness was elicited nor were there any palpable masses. Neither the liver nor the spleen was palpable.

The skin over the left forearm on the extensor surface presented a dry, erythematous area which had been present for months and looked like an eczematous lesion.

The extremities were normal. There were no other noteworthy findings in the routine physical examination.

Blood Hemoglobin 75 per cent R B C 3,180,000; W B C 21,450. Differential Count Polymorphonuclears 63 per cent, lymphocytes 31 per cent eosinophiles 5 per cent.

Urine Straw color sp gr 1.024 cloudy, reaction alkaline, few white blood corpuscles, amorphous phosphates, trace of albumin no sugar or diacetic acid.

X-ray Examination The frontal sinuses were not developed. The ethmoids were not aerated. The maxillary antra were small and not well aerated. The right maxillary antrum was denser than the left. The sphenoid sinuses were not yet aerated. The sella turcica was normal.

The chest roentgenogram revealed a normal cardiac and aortic outline. The cardiophrenic angle was especially prominent on the right side because of the low diaphragm.

Skin Tests These tests were done in the Allergy Clinic and showed that the child was sensitive to chicken feathers, duck feathers horse dander, house dust, eggs radish rhubarb spinach, tomato mustard, herring ragweed (++++) and cocklebur.

Sputum Examination There were no tubercle bacilli. There were numerous gram positive diplococci bacilli, and short chain streptococci. Eosinophiles were present, but no Curschmann's spirals or crystals.

Clinical Diagnosis Asthma and epilepsy

COMMENT

This eight year-old girl is of a markedly allergic constitution (eczema, hay fever, asthma, skin tests) and, in addition, suffers from frequent epileptic seizures, which seem to be related in their incidence to the attacks of asthma. It is possible that these convulsive disturbances may be due to an alkalosis brought about by asphyxia during the asthmatic paroxysm. However it is quite possible that both the asthmatic and the epileptic symptoms may be due to the underlying allergic reaction.

The treatment has included calcium ephedrin belladonna, and attempts at desensitization against offending allergens. At times symptomatic relief is afforded but in general, the results of treatment thus far have not been very encouraging. Lately the use of sodium thio-sulphate has been resorted to with the purpose of altering the colloid state. This treatment was suggested by Lumiere and is based on

his experimental studies For the past three months there have been no epileptic seizures and two mild attacks of asthma However, it is too soon to make any critical comments on the thiosulphate therapy

SUMMARY

1 Attention is called to the very significant relation of the state of allergy to certain types of "idiopathic epilepsy"

2 A case report is presented of an allergic eight-year-old girl who has epileptic seizures in association with her asthma

3836 W ADAMS STREET

REFERENCES

- 1 Spangler, R H J Allergy 3 39, 1931
- 2 Rowe, A H J Lab & Clin. Med 13 31, 1927
- 3 Levin, S J J A M A. 97 1625, 1931
- 4 Pagniez, P, and Lieutaud, P Presse méd 27 693, 1919
- 5 Miller, J L Am J M Sc. 168 135, 1924.
- 6 Frugoni Polichinico 29 179, 1922
- 7 Lumiere, Auguste Rôle des Colloïdes Chez les Etres Vivants, Paris, 1921, Masson et Cie

THE USE OF WHOLE CITRATED BLOOD INTRAMUSCULARLY IN A MEASLES EPIDEMIC

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PROVIDENCE, R I

IN January and February of 1932 there occurred in Providence, R I, a widespread epidemic of measles. The epidemic was a mild form of the disease, and did not tend to cause complications. The available supply of convalescent serum was soon exhausted and the paucity of adult cases during the epidemic prevented a replacement of the supply. Physicians were therefore unable to obtain serum for use on the younger children exposed to this disease, and in a number of cities and towns were forced to use blood acquired from the convalescent cases in the homes, or in a few instances from parents who had the disease either in childhood or in youth.

The total number of cases in January and February, 1932, reported to the Providence Board of Health was 4,827, with only 10 deaths during these months. I wish to report 89 cases which were given whole citrated blood direct from the donor to the recipient in the homes. The method of administration was to draw 3 c.c. of sterile 2 per cent sodium citrate solution into a 30 c.c. syringe and withdraw from one of the veins in the donor's arm anywhere from 5 to 25 c.c. of whole blood. This was injected intramuscularly into the external aspect of the left thigh of the recipient about midway between the great trochanter and the external condyle of the femur.

The average time of injection was four days after the rash occurred in the patient to whom the child was exposed. The average amount injected was 20 c.c. The majority of the donors were brothers or sisters recovering from measles and the blood was not taken unless the donor's temperature had been below 100° F. for forty-eight hours and no complications were present. In 14 cases 25 to 30 c.c. of the parent's blood who had had measles from ten to thirty-five years previously was used. The age of the recipients varied from four months to eleven years. After the blood was given the parents were instructed not to carry out any precautions as to isolation except in four instances where the blood was given to infants under one year old.

I have separated these 89 cases into 4 different groups because they consist of the observations of 4 different pediatricians. All of the recipients in Groups 1 and 2 were exposed to other members of their own families, only one patient being exposed to a schoolmate and in this case the recipient showed definite signs of measles. In this way

it is possible to evaluate the severity of the cases treated with whole blood as compared with the untreated cases in these families. I realize that this evaluation of necessity must be a matter of personal judgment and may be open to criticism.

The first group of 29 cases are from my own practice and were under my personal observation. I have classified the average case not treated with whole blood during this epidemic in the following way: temperature 102°-104° F, conjunctivitis 3-plus, rash 3-plus, cough 3-plus, and duration four days. The cases which were treated with whole citrated blood are shown in Table I.

TABLE I

NAME	HIGHEST TEMP	CONJUNCTIVITIS	RASH	COUGH	DURATION IN DAYS	COMPLICATION
A H	101	0	+	0	2	0
D W	103	0	++	+	2	0
S L	101	+	+	0	1	0
D D	103	+	+	+	2	0
R K	101	0	+	0	1	0
C K	102	+	++	+	2	0
L	100	0	+	0	1	0
A C	100	0	+	0	2	0
E C	100	0	+	0	2	0
J C	105	++	+++	++	3	0
B C	100	0	++	0	2	0
D G	High	0	++	0	1	0
N O'N	105	+	++	+	1	0
N F	100	0	+	0	1	0
B G	101	+	+++	0	1	0
D G	High	+++	+++	+++	4	0
P D	101	0	++	+	2	0
C O	99.6	0	+	0	1	0
T H	101	0	+++	0	2	0
A C	98.6	+	++	0	1	0
R C	?	0	++	+	1	0
E K	99.6	0	++	0	1	0
R K	99.6	0	++	0	1	0
R V	99.6	0	++	0	1	0
V S	99.6	0	++	0	1	0
J W	101.6	0	+	+	2	0
W K	102	+	++	++	2	0
C K	102	+	++	++	2	0
C M	102	0	+	+	2	0

The second group, 38 in number, are tabulated from the records of my associates and from the observation of the parents, asking them to compare the donor and the recipient as to comparative severity of the measles. In every instance the donor was older than the recipient and would be expected to have a milder case than the recipient. The terms used in this group are as follows: "Mild" means slight conjunctivitis, slight cough, temperature not over 102° F and a generalized rash. "Severe" means a typical case of photophobia and conjunctivitis, irritative constant cough, temperature 102° to 104° F, generalized confluent rash. There were 24 mild cases and 6 severe cases.

Of the latter 3 patients had received but 5 cc to 10 cc of whole citrated blood. Eight cases did not contract measles at all but were exposed thoroughly and no precautionary isolation was attempted.

The third group consists of 17 cases in an orphanage. One of my associates took 8 ounces of citrated blood from one donor, a girl who had had measles within eight weeks and gave about 10 cc to 15 cc to each of the children. These children had been exposed twice in a nursery. The first exposure and the second exposure were about eighteen days apart. None of these children had had measles. They varied in age from eighteen months to four years. Ten developed very light cases while 7 did not have measles at all.

In a fourth group I wish to give in more detail a summary of the manifestations of measles which occurred in 5 cases, because in this way some of the points which I wish to emphasize in the use of whole citrated blood as a therapeutic measure of great value in lessening the severity and preventing the complications of measles can be pointed out.

CASE 1—Earl M., a twin eleven years old developed measles rash Dec. 25 1931. Temperature 101 to 102 F. marked photophobia and conjunctivitis severe confluent rash all over his body marked cough, but no chest signs. He recovered in four days but coughed for one week. On Dec. 29 when his temperature was 98, 20 cc. of whole blood was taken from him and injected into the left thigh of Florence M., a twin sister. On Jan. 5 1932, Florence started with a slight cough and temperature 101 to 102. On Jan. 6 she had a generalized severe confluent measles rash all over her body which appeared within twelve hours. Temperature 101 F. On Jan. 7 there was a sudden drop in temperature to 99 during the night and the cough disappeared in forty-eight hours.

This case indicates I think, that even in older children whole blood may influence measles to a marked degree.

CASE 2—Barbara W. three and a half years old, was exposed to Marshall W. on Jan. 7, 1932. Marshall W. had a temperature of 101 to 103 F., with severe conjunctivitis moderate cough, marked rash and no signs in the lungs. On Jan. 10 when his temperature was 98.8 20 cc. of whole blood was taken and injected into the left thigh of Barbara W. On Jan. 10 ten days after the brother's rash and six days after the injection of the blood Barbara W. began limping and complaining bitterly of pain in the left leg. On physical examination she was very tender over the outer aspect of the left thigh and passive or active movement of the leg was impossible. The temperature was 101 F. There was no bone thickening. On Jan. 19, she was less tender, and on Jan. 20 a faint typical measles rash came out all over the body. The temperature came down to normal and the leg was much better as soon as the rash came out. There was no conjunctivitis photophobia, or cough.

This case was interesting in that the symptoms referable to the leg were severe and were undoubtedly a reaction to the donor's blood localized to the region of injection and were very likely due to the onset of the disease itself which the serum of the whole blood succeeded in aborting.

CASE 3—Chester W., aged five years, the brother of Thomas W. had a typical measles rash with bad cough and conjunctivitis on Jan. 21, 1932. An attempt was made to take blood from him on Jan. 25. This was unsuccessful and so 25 cc. of

whole blood was taken from the mother, who had had measles about twenty years previously. This blood was injected in the left thigh of Thomas W. On Jan. 31, ten days after his brother's rash and six days after the injection of the whole blood, he had severe pain in his left leg and was unable to move it. A typical measles rash broke out on Feb. 1 with temperature of 101° to 103° F. On appearance of the rash the pain in the leg disappeared. There was no conjunctivitis, very slight cough, and within twenty-four hours the rash faded and the temperature dropped to 100°.

This case illustrates the use of whole citrated blood from the parent with a similar local reaction to that which occurred in Case 2, where recent convalescent blood was used.

CASE 4—Sally L., five years old, was exposed in school to the child who sat next to her on Jan. 16, 1932. The schoolmate had a moderately severe case of measles with temperature 102° to 104°, she was sick four days, threatened with otitis media and had a cough persisting for one week. On Jan. 23, seven days after exposure, Sally L. was given 25 cc of paternal blood in the left thigh. The father had had measles twenty-eight years previously. On Jan. 30, Sally L. had a temperature of 101°. On Jan. 31, she had a faint generalized measles rash and a temperature of 100°, the next day the patient was well.

In this particular case the measles was influenced to a very marked degree. The father is a pediatrician and whether the potency of his blood was due to constant exposure to the virus of measles is an interesting question.

CASE 5—R. E. G., Jr., aged two and a half years. On Jan. 30, 1931, R. E. G.'s sister had a typical measles which ran a mild course. Two days later 20 cc of whole blood taken from the father, who had had measles twenty-two years ago when twenty years of age, was injected in the thigh. No attempt was made to isolate this child and he ran in and out of his sister's room, sometimes actually crawling over her bed. Ten days after administration of the whole blood he developed a temperature of 104° F. "Vomited, had pain in the left leg, was unable to move it. The next morning he was perfectly well, except that he had a blotchy rash all over the left leg." Two weeks after the first case an older brother and sister who had not had any blood injected, developed severe measles which lasted for eight days, with a temperature of 101° to 104° F. The brother, thirteen years of age, had a definite otitis media in one ear which was incised and drained for one week. No attempt at isolation was made from these two cases and R. E. G. was exposed constantly to his brother and sister. He never developed any other symptoms of measles than those mentioned after the first exposure.

This case speaks for itself. It is difficult to believe that there are any two-year-old children who are inherently immune to measles and this would be the only explanation possible unless the father's blood had conferred upon him a partial immunity.

I therefore believe that it is very worth while to use whole citrated blood in the manner which I have described in this article to protect children from three months to six years of age from the complications which are very liable to follow measles. I do not believe in giving whole blood until three to four days after the rash appears in the case to which the child has been exposed, because if done earlier than this it may prevent any signs of measles, and the immunity thus conferred will last only a short time. There is also a psychologic ad-

vantage of using blood obtained from the patient's own family instead of the serum supplied by the health department coming as the serum does from unknown donors. It is probable that the attenuated measles which occurs may protect these children for life, or at least carry them through the years in which they might develop complications of a more or less serious nature.

I wish to express my appreciation to Dr. Henry E. Utter, Dr. William P. Buffum, and Dr. Reuben C. Bates for allowing me to use their cases in this article.

122 WATERMAN STREET

ANTIQUES OF PEDIATRIC INTEREST

T G H DRAKE, M B, F R C P (C)

THE ceremony of touching for scrofula, the King's Evil, was performed in England from the time of Edward I until the end of Queen Anne's reign (with the exception of during the reign of William and Mary), a period of nearly 700 years

In the reign of Henry VII, the presentation of a piece of gold was first generally introduced. This was the angel noble, a circulating gold coin of the time, on which an angel is represented standing with both feet on a dragon. A warrant issued in the reign of James I for the special coming of angels as touch pieces shows that although they were current coin, they were also made ready pierced for the purpose of suspension about the sufferer's neck during the ceremony of touch



Gold touch piece, Charles II, circa 1662 (diameter $\frac{1}{8}$ th inch)

ing From the days of Charles II to those of Queen Anne, this gold coin being no longer current, a special gold medalet of the type illustrated, varying only in size and the name of the reigning sovereign, was struck and perforated for the ceremony

The immense popularity of the ceremony is shown by the entry in *Evelyn's Diary* for March 28, 1684 "There was so great a concourse of people with their children to be touch'd for the evil, that six or seven were crush'd to death by pressing at the chirurgeon's doore for tickets "

The following is Evelyn's description of the ceremony

"6 July, 1660 His majestie began first to touch for ye evil, according to custom thus his majestie sitting under his state in ye banquetting house, the chirurgeons cause the sick to be brought or led up

From the Department of Pediatrics University of Toronto and the Hospital for Sick Children Toronto

to the throne, where they kneeling, ye king strokes their faces or cheekes with both his hands at once at which instant a chaplaine in his formalities says, He put his hands upon them and he healed them. This is said to every one in particular. When they have ben all touch'd they come up againe in the same order, and the other chaplaine kneeling, and having angel gold strung on white ribbon on his arme, delivers them one by one to his majestie who puts them about the necks of the touch'd as they passe, whilst the first chaplaine repeats, 'This is ye true light who came into ye world.'

The register of those touched for the King's Evil by Charles II extends from May, 1662 to April, 1682 and gives the number of persons touched by the king for the evil as 92 107, as many as 600 being touched at one ceremony.

Belief in the efficacy of the royal touch for the cure of scrofula was not confined to the ignorant. Richard Wiseman in *Severall Chirurgicall Treatises*, 1676, writes

"But it is not my business to enter into divinity controversies, all that I pretend to is first the attestation of the miracles and secondly, a direction for such as have not opportunity of receiving the benefit of that stupendous power."

And the following is his answer to those who questioned the miraculous cure

'For since it cannot be denied that many go away cured some will impute it onely to the journey they take, and the change of air, others to the effects of imagination and others to the wearing of gold

"The first of these is easily confuted by the hundreds of instances that are to be given of inhabitants of this city who certainly could meet with little change of air, or indeed of exercise, in a journey to White hall. The second is readily taken off by the examples of infants, who have been frequently healed, though they have not been old enough to imagine any thing of the majesty, or other secret rays of divinity, that do attend kings, or do any other act that way to contribute to the cure. The third hath more of colour in it because many that have been touched, have upon loss of their gold felt returns of their malady, which upon recovery of that have vanished. But in this case also we have many evidences of the contrary

"For his Majesty's royall father in his great extremity of Poverty had not gold to bestow, but instead of it gave silver and sometimes nothing, yet in all those cases did cure, and those that were cured by his blood wore no gold

"Now whereas upon the loss of the gold some have found damage, I would know, whether any of them were relieved by the wearing any other gold *then* what the king gave them."

Critical Review

ALLERGY AS RELATED TO OTOLARYNGOLOGY AND PEDIATRICS

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IN A PREVIOUS review in this Journal, Smyth¹ made a comprehensive survey of the most important articles appearing in the literature on the subject of allergy in general. In another review, Dean² gave an interesting account of the recent advances in pediatric otolaryngology. In the present review, it is intended to make an analysis of those publications having a relationship to both the otolaryngologist and the pediatricist. The commonest manifestations of allergy are those which occur in the nose and paranasal sinuses, and while this area may be the only site involved, allergy is frequently manifest in other parts of the body and in other ways. It is often necessary for the otolaryngologist to determine whether some condition such as headache, gastrointestinal disease, bronchitis, asthma, eczema or recurrent colds, as diagnosed by the pediatricist, is associated with a nasal allergy. The presence of a definite nasal allergy should suggest the allergic origin of the various conditions mentioned.

The responsibility of diagnosis and treatment of certain infections of the upper respiratory tract in children, such as acute and chronic rhinitis, sinusitis, tracheitis, bronchitis and laryngitis, should rest on both the otolaryngologist and the pediatricist. Although these disturbances may be due to infection, they are frequently manifestations of allergy, and if proper treatment is to be instituted, the infections must be differentiated from those conditions of an allergic nature. It must also be emphasized that an infectious process may occur in a child known to be allergic, so that attention should be directed to this factor as well as to the infection. The points relating particularly to coexisting allergy and infections in adults have been emphasized in former communications^{3, 4, 5, 6, 7}. In the Pediatric Allergy Clinic of the Washington University Dispensary, we have had opportunity to observe a large number of children with seasonal and nonseasonal nasal allergy with and without associated bronchial asthma. Cases of eczema and selected cases of gastrointestinal disease, headache, frequent head colds, paranasal sinusitis, recurring acute bronchitis, chronic bronchitis, bronchiectasis and various forms of dyspnea, have been observed with the idea of determining whether or not allergy was a factor in the production of these conditions. In many of these cases the diagnosis of an associated nasal allergy suggested the allergic origin of the other condition. It was found that it is especially important in dealing with the respiratory conditions to determine whether we were dealing with a pure allergy, an infection or an allergy with superimposed infection. A proper diagnosis of these various conditions and their relation to allergy can be established only after taking a detailed clinical history and making certain physical and laboratory examinations.

Reference to the relationship of allergy to infection may be found only in the most recent literature on the subject of frequent colds, sinusitis, and bronchitis. The relationship of sinusitis and acute nasal infections to asthma and other forms of allergy has been greatly clarified by a careful study of the differential diagnosis between allergy and infection, and has been emphasized by Dean,⁸ Carmack,¹⁰ Richards,¹¹ Brown,¹² Cassady,¹³ and McLaurin.¹⁴

Cohen and Rudolph¹⁵ in a recent report emphasized the importance of differential diagnosis between allergic and infectious conditions of the upper respiratory tract in children.

Consideration must be given to the factors which indicate the allergic basis for the complaints. These are (1) the family history, (2) past history of allergy, (3) presenting symptoms, (4) skin tests and (5) blood examination for eosinophilia. From the otolaryngologic standpoint, the following factors are to be especially considered: (1) the nasal symptoms, (2) rhinoscopic examination, (3) nasal smears, (4) roentgenologic examination of the sinuses and (5) histologic examination of the nasal and sinus tissues.

A detailed clinical history in these cases is of the utmost importance. A study of the family history of allergic patients will reveal the fact that a much larger number of relatives are found to be affected with manifestations of allergy than is the rule in other families. The studies of Cooke and Vander Veer,¹⁶ Spain and Cooke,¹⁷ Adkinson,¹⁸ and Balyeat,¹⁹ show positive family histories in 40 to 60 per cent of the asthma cases in their series. Among the normals, investigated in some of these studies, a positive family history occurred in only 7 to 9 per cent. Coca²⁰ and his associates have pointed out that heredity not only plays a part in the choice of the individuals affected, but also more or less determines the nature of the malady by designating the predisposed shock organ. The evidence seems to indicate that the age of onset is more or less predetermined by hereditary factors as is also the nature of the atopsens or allergens to which the patient tends to become sensitive. Cooke and Spain,²¹ and Cooke²² have reported that when there is a positive history of allergy in both parents, approximately 75 per cent of the offspring will develop manifestations of allergy before the tenth year. With a single inheritance 31 per cent, and with no history of inheritance 20 per cent develop manifestations before the tenth year. Of all children with bilateral inheritance 70 per cent will eventually develop symptoms and of those with a unilateral history about 50 per cent. The earliest manifestation of allergy which appears in infancy is eczema. This is often replaced by the respiratory symptoms later. During the first three years of life foods are the outstanding factors and after this age the inhalants are to be considered. Hypersensitivity to foods and infections in infants, tends to disappear between the age of five and ten years but hypersensitivity to the inhalants tends to persist. According to Rowe,²³ however, food sensitization may remain as a major factor or the sole cause of symptoms into adult life, in spite of the fact that skin tests may be negative. Asthma developing between the age of three and thirty years is usually caused by the inhalants. The onset is often gradual and is usually preceded by the nasal manifestations. Asthma appearing after the age of thirty years is usually associated with infections and is also gradual in its onset. The clinical history frequently shows that the allergic child has other manifestations of allergy such

as eczema, urticaria, gastrointestinal symptoms, asthma or hay fever, either recently or in the past. In some cases, the manifestations of the food allergies are not acute and lead to evidences of mild disturbances such as anorexia, malnutrition, nervous irritability and sleeplessness. The examination of the blood usually shows an eosinophilia and positive skin tests are usually found. In the infectious cases due to infection without allergy, the family history is usually negative for hypersensitive individuals, rarely are there any other manifestations of allergy, the blood shows no significant eosinophilia and skin tests are negative.

Since the clinical picture of acute rhinitis and acute paranasal sinusitis is well known, only a brief consideration of this phase of the subject is necessary. Attacks of acute rhinitis usually run a typical course, lasting from five to twelve days, after which there is usually an immunity lasting several weeks or if the attack is uncomplicated, there is a complete resolution of the process. There is generally a history of physical exposure or of contagion. The attack is accompanied by fever, malaise and other well-known symptoms. The onset is not related to food or inhalant contacts. The examination of the nose shows a swollen, usually hyperemic membrane with mucopurulent secretion which shows the presence of numerous pus cells. Roentgenograms of the sinuses are not often significant. When acute rhinitis does not undergo resolution within a reasonable period of time, however, a complicating sinusitis usually manifests itself with the symptoms of persistent mucopurulent discharge, positive roentgenographic findings and general symptoms of infection. In chronic paranasal sinus infections, it is particularly important to differentiate between allergy and infection and to take into consideration that an existing chronic infection may be associated with an allergic process.

It is also important to mention that the manifestations of allergy may be noted for the first time following one of the common contagious diseases of childhood. Peshkin²⁴ found that pertussis was the most frequent causative disease. Measles and scarlet fever were also mentioned. Other infections such as pneumonia and influenza may also be responsible. What appears to be a sinus infection following these diseases should, therefore, be carefully investigated because of the fact that nasal allergy may originate in this manner.

In the consideration of allergy as it manifests itself in the nose and paranasal sinuses in children, information in the history regarding the criteria which characterize the state of hypersensitivity must be obtained, but in the analysis of the clinical history, physical and laboratory findings, one may expect great variations. Sometimes diagnosis is prompt and easy but often it can be established only after periods of observation. We usually think of the nasal symptoms as being characterized by attacks of sneezing, nasal obstruction and the discharge of serous or mucous material. Picking at and itching of the nose, rubbing of eyes and clearing the throat or a dry cough may be prominent and characteristic symptoms. There are a great many instances, however, in which all of these symptoms are not present. Although sneezing may be a prominent symptom, in children it is frequently absent. The child may show only signs of nasal obstruction and nasal discharge. Obstruction may be more or less constant or it may be intermittent. Discharge may be profuse and watery or it may

be entirely postnasal in the form of thick mucus. A child may exhibit only the symptoms of transitory attacks of nasal obstruction. Attacks of nasal allergy are usually not related to contagion but frequently appear with an inhalant or food contact. Fever or constitutional symptoms are rarely present. Typical attacks are usually recurrent every few days or every few weeks. In certain cases however they may appear with long periods of remission resembling in this respect attacks of acute rhinitis. It is important to note other manifestations of allergy may exist in other parts of the body with those in the nose. Children often have gastrointestinal symptoms such as gas, belching, distention, cramps pain or diarrhea at the same time. Local or generalized headache, angioneurotic edema, bronchitis or asthma may also occur. Attacks of nasal allergy may alternate with attacks of acute rhinitis. Following an attack of acute rhinitis or bronchitis nasal symptoms may become more severe or they may entirely subside for several weeks. Acute infection frequently increases the degree of hypersensitivity in allergic individuals often precipitating symptoms after a period of apparent quiescence. The patient therefore may react to a slight exposure which in the absence of infection would not be sufficient to cause symptoms. Nasal symptoms may subside during the existence of some other manifestation of allergy such as urticaria. Nasal symptoms may be present or absent with allergic headache. During attacks of nasal allergy we must bear in mind that reactions are also occurring in the paranasal sinuses. The swelling of the lining membranes, the increase flow and consequent retention of secretions may produce local pain or headache.

On examination of the nose in allergy characteristic changes in the mucous membrane are found. They are characterized by a pale swollen edematous appearance of the turbinates and an abundance of mucoid secretion. Gross polypoid changes are rarely present in young children but may be found not infrequently in older children. During the state of active symptoms these changes are easy to recognize but during the quiescent periods the membrane may appear quite normal or may appear pale and dry with thick mucoid secretion, and the picture may not be easy to recognize.

The most important laboratory method used in diagnosis is the microscopic examination of the nasal secretions for the presence of eosinophiles. In the collection of nasal secretion for examination it is necessary to obtain mucous material because it contains the cells which are to be examined. Thin watery material usually shows very few if any cells. In children instead of swabbing the secretion from the nose simply direct the child to blow the nose on some waxed paper and transfer the material to glass slides. It is advisable to make two or three smears because the eosinophiles may be found only in certain parts of the specimen. They may be entirely missed upon the examination of only one slide. The smears should be stained by Wright's stain in the same manner as blood films. The number of eosinophiles observed may not be constant because several factors which cause them to appear may vary. During the complete inactivity, they should be absent. Frequently however during an apparent stage of inactivity, there are mild transitory reactions which do not give rise to noticeable symptoms yet the secretions will reveal the presence of many eosinophiles. If an acute infection occurs they may be either present or absent. They may be found in considerable numbers along with the

pus cells or neutrophiles, or due to the relatively large number of pus cells, they may appear diminished. As the cold subsides, the pus cells disappear and the eosinophiles continue and reappear in relatively increased numbers. In some cases, however, there may be few or no eosinophiles during an acute rhinitis. In these cases, the manifestations of allergy may entirely disappear for a certain period of time following the subsidence of the acute infection. The gross examination of secretions without cytologic study has proved to be very unreliable in drawing conclusions as to the presence or absence of pus. Clear secretion may show pus cells or eosinophiles or both. Yellowish mucopurulent secretion may contain pus cells, both types of cells, or may show only large numbers of eosinophiles.

If a chronic infection of the paranasal sinuses becomes associated with an allergic process, both eosinophiles and pus cells are found in the secretions. An exacerbation of the infection may result from repeated acute infection or from allergic reactions following contact with an offending allergen. Allergic reactions may cause considerable increase in an already existing edema.

In the histologic examination of the nasal tissues in allergy, in infection, and in allergy with infection, the picture is comparable to the cytology of the nasal and sinus secretions. Edema of the tissues is an almost constant finding in allergy and is usually very marked, but it may also be present with infection. Eosinophilic infiltration of the tissue is a characteristic feature of allergy, while acute rhinitis is characterized by some edema and neutrophilic infiltration. In combined allergy and infection, both types of cells are found. Lymphocytic and plasma cell infiltration are present in both types of reactions. Chronic infection produces connective tissue proliferation in various degrees.

The roentgenographic findings in the paranasal sinuses in allergy as well as in infection, are positive in a very large percentage of cases and cannot be differentiated from each other. In allergy, positive findings may be purely transitory, being present at one time and absent at another. It is unfortunate that in many of the reports in the literature on paranasal sinus infection in children, so much reliance has been placed upon roentgenographic findings and the cytology of the secretions has been so greatly neglected.

Too much reliance should not be placed on the performance of skin tests and their interpretation in the diagnosis of allergy. A positive reaction indicates nothing more than a clue as to past, present or future possibilities. Its significance must be determined by further clinical observation. On the other hand, negative tests do not rule out the possibility of existing allergy. Kahn,²⁶ for example, has found that skin tests in infants and young children, suffering with pollen asthma and hay fever, are frequently entirely negative or only slightly positive. He believes that such weak positive tests actually indicate a minor degree of hypersensitiveness and he urges that advantage can be taken of this low degree of sensitiveness in initial or early stages of asthma to render these children free or nearly free from attacks by proper precautions against pollen overdosage.

In the management of acute and chronic tracheobronchial conditions in children, the otolaryngologist is frequently called upon to determine the possible relationship to certain pathologic disturbances in

the nose and throat Cooke²⁷ has described a peculiar cough which he frequently found associated with allergic coryza. The cough is violent and paroxysmal in nature and is frequently accompanied by vomiting. He believes it is caused by hypersensitiveness and discusses the difficulty of differentiating this cough from pertussis. Duke²⁸ has also called attention to the occurrence of allergic bronchitis and states that it is often incorrectly diagnosed as tuberculosis, chronic bronchitis and bronchiectasis. A Brown² asserts that a spasmodic bronchitis sometimes inaugurates an attack of asthma in children. He believes that in children this type of bronchitis occurs more frequently than true bronchial asthma. Rowe²² Colmes²⁵ Colmes and Rackemann²⁰ and Kahn²⁰ state that a dry irritating cough is a symptom of sensitization of the trachea and the bronchi and point out the importance of recognizing these atypical cases of asthma. The examination of the nose in these cases may show the picture of allergy or infection. Attacks of asthma may follow immediately an attack of nasal allergy. An acute infection of the nose may also precipitate an attack of allergic bronchitis or asthma. Walzer²³ states that when infection precipitates attacks they usually occur several days after the onset of the infection, while in cases of pure allergy the attacks usually are produced immediately. The presence of upper respiratory infection, therefore, such as the common cold, paranasal sinusitis and tonsillitis is often responsible for the precipitation of an allergic bronchitis or asthma. The proper treatment of these upper respiratory conditions increases the resistance of the patient and prevents the occurrence of the infections and thereby simplifies the management of the allergy.

In the treatment of these cases it is evident that the control of the allergy is of primary importance. An attempt should be made not only to eliminate the offending allergenic substances but to eliminate if possible all nonspecific factors. The nutritional state of the patient should receive due consideration. All infection such as that existing in the paranasal sinuses, teeth, tonsils and adenoids should be eliminated in cases in which these procedures are indicated. In the performance of surgical procedures it is particularly important to avoid the stages of active allergic symptoms, this is especially true regarding active hay fever. All cases of allergy should be under control before resorting to surgery. In children, as well as in adults, the observations of Rackemann and Tobey,³¹ Bullen²² and others have shown that in a large series of cases the removal of the tonsils and adenoids has shown no definite influence in the improvement of the existing asthma.

Walzer²³ states that the removal of the tonsils and adenoids in an allergic individual is frequently followed by the development of nasal allergy or asthma or both. Many cases of pollen hay fever or asthma date the onset of their first symptoms from a tonsillectomy and it is impossible to consider the coincidence of the two conditions or events as purely accidental. The question may well be raised as to whether the infection which instigates the procedure may not have been responsible rather than the operation itself. We have found that in many cases of children with allergy a tonsillectomy was definitely indicated, but with careful attention to the control of the allergy the occurrence of untoward complications could be avoided with reasonable safety.

REFERENCES

- 1 Smyth, T S Allergic Diseases, J PEDIAT 2 349, 1933
- 2 Dean, L W Recent Advances in Pediatric Otolaryngology, J PEDIAT 1 379, 1933
- 3 Hansel, F K Clinical and Histopathologic Studies of the Nose and Paranasal Sinuses in Allergy, J Allergy 1 43, 1929
- 4 Hansel, F K Allergy as an Etiologic Factor in Paranasal Sinus Disease, J Missoury M A 27 275, 1930
- 5 Hansel, F K Allergy and Its Relation to the Inflammatory Diseases of the Nose and Paranasal Sinuses, Ann Otol Rhin & Laryng 39 510, 1930
- 6 Hansel, F K Diagnosis and Treatment of Allergic Disease of the Nose and Paranasal Sinuses, Tr Am Acad Ophth & Otolaryng 35 343, 1930
- 7 Hansel, F K Treatment of Allergy of the Nose and Paranasal Sinuses, Tr Am Laryng Rhin. & Otol Soc 36 403, 1931
- 8 Dean, L W Nasal Sinus Disease in Small Children, Laryngoscope 40 371, 1930
- 9 Dean, L W The Relationship between Infections of the Upper Respiratory Tract and Pediatric Conditions, Ann Otol, Rhin & Laryng 39 670, 1930
- 10 Carmack, J W Sinusitis in Children, Ann Otol, Rhin & Laryng 40 515, 1931
- 11 Richards, L The Prognostic Significance of Sinusitis in Children, Ann Otol, Rhin & Laryng 40 1076, 1931
- 12 Brown, J M Sinusitis in Children, Ann Otol, Rhin & Laryng 38 500, 1929
- 13 Cassady, J V Sinus Disease and Chronic Cough, Laryngoscope 40 615, 1930
- 14 McLaurin, J G Chest Complications of Sinus Disease, Ann Otol, Rhin & Laryng 41 780, 1932
- 15 Cohen, M B, and Rudolph, J A Allergic and Infectious Conditions of the Upper Respiratory Tract in Children, J A. M. A 97 980, 1931
- 16 Cooke, R A, and Vander Veer, A, Jr Human Sensitization, J Immunol 1 201, 1916
- 17 Spain, W C, and Cooke, R. A Studies in Specific Hypersensitiveness II The Familial Occurrence of Hay Fever and Bronchial Asthma, J Immunol 9 521, 1924
- 18 Adkinson, J The Behavior of Bronchial Asthma as an Inherited Character, Genetics 3 363 1920
- 19 Balveat, R M Acquisition of Specific Hypersensitiveness Based on a Study of 1,000 Asthma and Hay Fever Cases, South M J 21 554, 1928
- 20 Coca, A F Studies in Hypersensitiveness, Influence of Heredity in Atopy, J Lab & Clin. Med 12 1135, 1927
- 21 Cooke, R A, and Spain, W C Studies in Specific Hypersensitiveness XI. The Familial Occurrence of Hay Fever and Bronchial Asthma, J Immunol 9 521, 1924
- 22 Cooke, R A Asthma and Preasthmatic Conditions, M J & Rec 122 539, 1925
- 23 Rowe, A H Food Allergy, Its Manifestations, Diagnosis and Treatment, Philadelphia, 1931, Lea & Febiger, p 177
- 24 Peshkin, M D Asthma in Children. I. Etiology, Am J Dis Child 31 763, 1926
- 25 Kahn, L S Significance of Negative Skin Tests in Pollen Hay Fever and Asthma in Infants and Young Children, South M J 21 559, 1928
- 26 Duke, W W Asthma, Hay Fever, Urticaria and Allied Manifestations of Allergy, St. Louis, 1926, The C V Mosby Co
- 27 Brown, A Asthma in Children, Canad. M A J 12 780, 1927
- 28 Colmes, A Cough Due to Hypersensitiveness to Orris Root, New England J Med 200 389, 1929
- 29 Colmes, A, and Rackemann, F M Studies in Asthma IX Cough as a Manifestation of Human Hypersensitiveness, J A M A 95 192, 1930
- 30 Kahn, L S Essential Difference in Chronic Pollen Hay Fever and Asthma in Children and in Adults, J Lab & Clin Med 12 1197, 1927
- 31 Rackemann, F M, and Tobey, H G Studies in Asthma IV The Nose and Throat in Asthma, Arch Otolaryng 9 612, 1929
- 32 Bullen, S The Effect of Tonsillectomy in Allergic Conditions, J Allergy 2 310, 1931
- 33 Coca, A F, Walzer, M, and Thommen, A A Asthma and Hay Fever in Theory and Practice, Baltimore, 1931, Chas C Thomas, p 214

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MONDAY AFTERNOON SESSION

JUNE 12, 1933

Round Table Conference on Allergic Conditions

Leader Dr Bela Schick, Assistant Dr J E Gonce

DR SCHICK.—It is my intention to make only short introductory remarks. I would like to have a very lively discussion which need not be limited to the problems I shall mention.

When one talks about allergy, it should be remembered there are two things to be considered: First, allergy as a very wide term meaning all kinds of altered reactivity of the organism due to previous administrations of a foreign substance. Every disease both the acute ones and to a greater extent all chronic diseases, may show allergic features. Second, we can include in our discussion the so-called allergic diseases such as asthma, hay fever, eczema, urticaria, etc. A better title for these diseases would be 'hyperergic diseases.'

(Dr Schick abstracted his remarks as printed in the February 1933 issue of the JOURNAL OF PEDIATRICS.)

DR J E GONCE (Madison Wisconsin)—In opening the discussion of Dr Schick's summary on the general subject of allergy, I would like to emphasize the fact that the proper handling of cases of asthma hay fever eczema, etc., is an intricate procedure one which requires the closest attention to every detail and familiarity with the latest theories and practices of the specialists in this field of medicine. A casual interest in allergic disorders is certainly paralleled with bad results.

A few of the practical points connected with the diagnosis and treatment of allergic disorders which impress me as being of fundamental importance are concerned with (1) the selection of materials (2) the use of guides in pollen therapy and (3) methods of administration of protein extracts.

(1) The materials used for sensitization tests and for desensitization must be absolutely reliable. In my experience glycerosaline extracts are more sensitive but on account of the danger of causing constitutional reactions must be preceded by scratch tests thereby making their use too expensive for general use. Many specialists in allergic disorders use powders for scratch testing but most of these men manufacture their own in order to be certain of their allergic activity. Where it is impracticable or impossible to prepare protein extracts for one's own use as is the case for most of us it is necessary to exercise the greatest care in the selection of a commercial manufacturer from whom to purchase extracts. In this connection an experience of mine last winter is enlightening. In answer to questions concern

ing the detailed preparation of pollen extracts, one well known firm replied, "In the beginning the writer would say that our house is probably not in any way different from any other commercial house and while we have no objection to offering the general routine of our methods of manufacture, nevertheless, there are many items connected with the manufacturing of proteins and pollens that are considered manufacturer's secrets." Another house hedged on some of the questions and the third firm addressed completely answered all questions and denoted their willingness and even desire to supply all information within their power to furnish. Now that Stull and Cooke and their coworkers seem to have definitely shown that the allergically active factor of pollens resides in the albumin fraction and have suggested the standardization of pollen extracts on a protein nitrogen basis, it is quite likely their recommendations will be accepted and the preparation of various extracts for testing and therapeutic purposes become a uniform and reliable procedure practiced by all commercial houses alike.

In regard to the stability of extracts prepared for therapeutic purposes, I believe everyone at the present time agrees that the glycerosaline extracts are the most stable. In a recent issue of the *Journal of Allergy*, it is stated that 31 out of 73 specialists use extracting fluids containing glycerine.

(2) The use of various guides in pollen therapy is now a well established procedure and may be considered under three divisions. First, determination of the patient's skin sensitivity to serial dilutions of the offending pollen will prevent waste of time by an unnecessary number of weak doses and will also help to avoid the administration of initial doses large enough to cause constitutional reactions.

Second, application of skin tests in serial dilutions during the course of treatment is of decided value in estimating the frequency and number of doses necessary to bring about satisfactory desensitization in the individual case. Although it is not universally agreed that pollen therapy influences the severity of the response of skin tests, the opinion of many men, especially Dr. Duke of Kansas City and Dr. S. T. Brown of Washington, who use large doses, is that there is not only a relationship between pollen therapy and skin sensitivity but a diminution in skin tests may be indicative of a lessened clinical sensitivity as well. In proof of this belief, it has been shown that failure to obtain clinical improvement in a hay fever patient whose skin test has been changed by therapy from a strongly positive to a weakly positive or negative reaction, may be due to extra pollen sensitivity.

Third, the extent of the local reaction from each subcutaneous injection of pollen extract is of considerable help in estimating the dose of the following injections. In using this guide, it is necessary to place the injection superficially in the subcutaneous tissues because the deeper method of injection is less apt to produce a local reaction.

(3) As to the method of administration of protein extracts, I would like to encourage the use of the Duke method. Although there are certain specialists in allergic disorders who like to poke fun at the use of the tourniquet and adrenalin-ephedrin mixture, I feel quite certain this method makes the administration of protein extracts almost "fool proof." It has several advantages in that it permits rapid increase in the amount of protein extracts given, the administration of doses of a size far beyond those of the unmodified injection method, and, in the case of perennial treatment, permits the lengthening of the interval between injections to two, three or four weeks without danger of constitutional reaction. Dr. Duke himself says this interval may be stretched to two or three months.

I personally have dropped the use of the tourniquet because soon after adopting the Duke method of injection I noticed on the third, fourth or subsequent application of the tourniquet, the child's arm immediately became terribly discolored. Consequently, I leave off the tourniquet and minimize the possibility of injecting directly

into a blood vessel by first drawing back the plunger of the syringe before making the injection. The mixture of one-third adrenalin and two thirds ephedrin (8 per cent solution) in amounts of 0.3 c.c. combined with the extract causes an almost immediate blanching of the skin where the injection is superficially placed and the rate of absorption, I am sure is retarded just about as much as when the tourniquet is used.

I have only a couple more things to say. I happened to think when Dr Schick was speaking of status asthmaticus, that our adult medical service has had occasion to treat several patients with this condition by means of bronchoscopic cleansing of the trachea and bronchi. One patient is a traffic officer in Madison who obtains immediate relief by this treatment. He then remains free from symptoms for many months.

In closing I would like to ask Dr Schick to state his opinion of the relative merits of the ideas on tuberculosis of Heimbeck of Oslo and Myers and Stewart of Minneapolis.

DR SCHICK.—About the influence of repeated injections on the intensity of the skin reaction, it can be stated that a large dose may have an attenuating effect upon a following skin test. Similar observations are made in tuberculin treatment. Frequently a Pirquet test made twenty four hours after a large dose of tuberculin (1 mg) will be smaller or even negative. The Pirquet test will become positive again after an interval.

Asthmatic patients free from attacks for several years still may have about the same intensity of the skin reaction as at the time of attacks. Apparently the reactivity of the skin is dissociated so to speak from the asthmatic reaction of the respiratory tract. This may be due to treatment or to aging (maturing). An eczematous patient may lose his eczema and exchange the eczema for an asthma. Apparently the skin changes its reactivity and the respiratory tract starts to react in an abnormal way. In eczema and asthma we frequently find that when the eczema improves the asthma gets worse or as the asthma gets better, the eczema appears. There is an interrelation between the two organs the skin and respiratory tract. There can exist a complete dissociation so the eczema can disappear while the asthma remains. It is possible to obtain a very strong skin reaction to a certain protein although the asthma is not due to this protein or you can encounter just the reverse a relatively weak reaction (\pm reaction) to a protein which is responsible for the asthmatic attack.

As to the use of adrenalin and the tourniquet, these procedures are helpful both slow down the absorption. Adrenalin brings about a vasoconstriction the tourniquet compresses the lymph channels. In all cases where we suspect the patient is very sensitive to the substance to be injected, i.e. horse serum such procedures should be taken into consideration especially the use of the tourniquet. The same can be accomplished in an easier way by injecting higher dilutions of the substance.

The story of a policeman who was treated during his attacks by sucking out the plugs with the bronchoscope is very interesting. Of course bronchoscopy is a little more dangerous in children than in adults.

Concerning the idea of Heimbeck in Oslo as to whether it is better to be infected with tuberculosis and become reexposed or to be infected with tuberculosis with no previous tuberculous infection I read very carefully the article by Dr Stewart in which he expresses the latter theory. The prevailing theory is that the first infection with tuberculosis in a mild form immunizes to a certain extent against a reinfection later in life. The immunity of the adult against tuberculosis is based upon the effect of the preceding infection in childhood. In an institution for the treatment of tuberculosis in Oslo Heimbeck divided the nurses into two groups in the one were the tuberculin positive and the other, the tuberculin negative nurses.

He studied these two groups of nurses during their stay, as they were exposed to tuberculosis and found the nurses who had a positive tuberculin test on admission were better off in that not such a large number of them developed an active tuberculosis. Many more of the nurses who came in with a negative reaction indicating they had no previous infection with tuberculosis, developed active tuberculosis. He used this observation as a reason to introduce active immunization with B C G against tuberculosis among nurses and he was very much satisfied with it.

Dr. Stewart found in his examination of 10,000 school children that several children who did not show any form of tuberculosis for several years before, on exposure developed a very mild tuberculous infection. On the other hand, children who were positive before to tuberculin and had some calcified foci in their lungs, developed a very active tuberculosis.

I still believe that much depends on the quantity of tubercle bacilli entering during exposure. If an individual has been exposed to a very large amount of infection, this person is in danger whether he had a previous infection with tuberculosis or not. We are afraid of massive reinfections, as the immunity against tuberculosis conferred by a previous infection is only a limited one. It is sufficiently strong for a mild reinfection but it does not help against a very violent one. I think it is too early to accept Stewart's viewpoint as final. We may still adhere to the idea that a small first infection produces a certain amount of immunity against a new infection.

(Discussion by Dr. Bell not sent in for publication.)

DR. BLATT (CHICAGO).—Dr. Schuck, you expressed a thought I believe should be stressed a little more, namely, the relationship between allergic phenomena and infectious diseases. In 1911 when I worked in your dispensary in Vienna, you emphasized the fact that some of the kidney complications of scarlet fever were allergic. At that time, you expressed the thought that in all probability the glomerular nephritis coming on in the third week of scarlet fever was a secondary phenomenon not due to a local streptococcal infection but probably to an allergic phenomenon of streptococcal origin. I have always felt that expression was worth passing on and nothing in the interim has changed my belief in this statement.

I think the term "allergy" is not satisfactory, as it is applied now. It has seemed to me that all forms of dermatitis should not be classified as allergic even though they express somewhat similar phenomena. For instance, a dermatitis due to sun rays, a dermatitis due to an irritant, a dermatitis due to feathers, a dermatitis due to some other immediate contact agent, should not be classified with those allergic phenomena associated with changes in protein sequential to liver dysfunction or direct gastrointestinal absorption without liver detoxication. It is quite apparent that the same principles which underlie Besredka's attempt at immunization through systemic means is influencing us in our allergic immunization. As you stated, it is quite possible to apparently arrest the asthma and have the skin retain its tendency toward urticarial phenomena on an allergic basis. I think many of these so-called allergic phenomena are much more closely related to dermatitis and are inflammatory rather than primarily exudative.

Based upon findings of the United States Department of Agriculture, the milk shed of Chicago is definitely known and the open pasture has definite dates. In the spring when the cattle first are turned out to pasture, large numbers of weeds are ingested and many of these contain active glucosides which may be the source of some of our allergic skin phenomena such as hives and urticaria.

As to infection with tuberculosis, Dr. Jaffe has expressed himself as being in accord with Stewart's opinion and I am accepting this theory. The large amount of pathologic material at Cook County Children's Hospital seems to show many serious effects of superimposition of tuberculous infection rather than primary

sensitization and primary complex dissemination. Last winter I saw a number of postmortem examinations on generalized tuberculosis with a primary complex that was apparently entirely healed and I am of the opinion the primary vaccination with tuberculosis was not effective in protecting these cases. From time to time I have seen a general dissemination from a primary complex but these cases are comparatively rare.

I would like to ask a question in regard to the use of dextrose which reports from Guy's Hospital seem to favor. It is thought its effectiveness has to do with liver protection possibly that it has to do with increasing of the detoxified reaction in the liver rather than any relationship to the blood sugar content primarily. I tried this procedure in two or three cases, in one of which I had very unusual success. Not only did the patient an adolescent girl who had asthma all her life react favorably so far as the asthma was concerned, but she gained a large amount of weight.

DR. SCHICK.—The first question was about allergy in infectious diseases especially in scarlet fever. Dr. Blatt quoted me correctly. I believe that fourteen days or three weeks after the onset of scarlet fever a period of increased sensitiveness starts and all postscarlatinal diseases are the expression of this allergy (immediate) to a germ having survived from the time of the original scarlet fever process. Some authors feel that the first part of the scarlet fever process is also allergic in nature. I think my original idea is more correct that the first symptoms in scarlet fever are due primarily to a toxic substance and only the postscarlatinal diseases are allergic in nature. It is interesting that similar observations have been made in typhoid fever and measles. In order to be careful as to how far one should go with theories, I have left open the answer to the question whether the nephritis and the other postscarlatinal conditions are the effect of the streptococcus and its toxin.

Dr. Blatt pointed out that it is very hard to apply the term allergy to so many different types of symptoms and I agree. However allergy is a necessary term; we need such a word for the 'altered reactivity'. If we make clear that what is especially important from the practical viewpoint is the hyperergic or anaphylactic reaction there will not be much room for misunderstanding. Severe anaphylaxis, characterized by a shock endangering life does not occur so frequently. If one considers how many millions of injections of serum are given and how few cases of real anaphylactic shock are observed one will realize that it is fortunately very rare. Anyone who has seen such an anaphylactic shock will never forget it and will be very cautious thereafter in injecting serum, particularly intravenously.

The good effect of the injection of glucose is difficult to explain. It may be helpful in stimulating the function of the heart. Another factor may be the improvement of the liver function as during the anaphylactic shock, the glycogen of the liver disappears. The circulation also will be benefited by the supply of fluid.

DR. LEWIS WEBB HILL (BOSTON).—There is a large group of skin conditions in infancy we call infantile eczema and I am quite sure we are in reality dealing with a number of different, probably unrelated diseases. We must split apart this group as far as we can, by close observation of the skin and very careful study as to etiology for we never will get anywhere with infantile eczema until we do.

If one considers the history of dermatology in the last fifty or seventy five years one sees that is what is happening. The dermatologist of older times was confronted by an individual with a red skin eruption and he gradually noticed these skin eruptions were different. Scabies used to be called eczema, so did psoriasis and pityriasis rosea. We must go through the same process with our infantile

eczemas before we can really understand them. I believe 60 to 70 per cent of the cases of infantile eczema are of allergic origin but there are, as Dr Bell has said, a good many causative factors other than allergy. I think we must take fungus infestation into consideration. In adult dermatology at the present time, there is a tremendous interest in fungus infestation of the skin with the epidermophyton group and the *Monilia albicans* or thrush group.

I am very much interested in this as regards infants and children and am trying to determine by intracutaneous skin tests with various fungi, what cases can be put into the fungus group. The difficulty is that oftentimes food allergy and fungus infestation occur together and I am quite sure it is the allergic child who is especially susceptible to fungus infestation. This work is not far enough along at present to say definitely that we can, by means of skin tests or by any other method, determine exactly which cases are due to fungus infestation and which are not, because culturing the fungi from the skin means very little. Making scrapings of the skin and finding them under the microscope means little as they also occur on so many normal skins. Both of these methods are somewhat complicated for average use.

Skin tests with various fungi show a fair number of positive reactions and I have brought a few pictures of what would seem to be fairly typical fungus eruptions. These pictures all represent probable monilia infection, that is, thrush of the skin. I have had positive tests in cases one would certainly call ordinary "eczema." Fungus infestation, however, is probably of relatively small importance in infantile eczema and we must go back to allergy to account for most of the cases.

We should do skin tests on most cases of infantile eczema as we get a good deal of information. This is perhaps more theoretical than practical because a great many times we find by the skin tests nothing whatever to help us in the actual treatment of the child. A five-month-old baby who has never eaten an egg may give a strong test to egg white. That does not help much in the practical treatment of that baby, but it does tell us that the baby is allergic and I consider the reaction to egg white in young infants a stamp of allergy. It identifies that baby as being of an allergic constitution and as Dr Schick said, sensitization through the placenta is probably very common and I am quite convinced a great many cases of infantile eczema start by sensitization to egg white through the placenta.

Egg white is the most difficult of digestion of any protein and if one eats a raw egg, some of the egg white goes unchanged through the intestinal mucosa into the general circulation. Some time ago I got some serum from an egg sensitive child with eczema and injected a little into my forearm. The next day I ate some cookies and within fifteen to twenty minutes, a big wheal developed on my arm.

I made some passive transfer tests for a baby with very bad eczema, whose skin was so bad I could not do ordinary skin tests. I put into the arm of the baby's father about 30 injections of the baby's serum in very small amounts and unknown to me, this man was in the habit of eating a raw egg every morning for breakfast. He ate a raw egg the next morning and his arm was enormously swollen for two or three days and the reaction persisted for several weeks. The serum of an eczematous child sensitive to egg may be a powerful thing and if passive transfer tests are done, we must be careful to use only very small amounts of serum or to dilute the serum considerably before injection.

I use a type of skin scratcher that I devised. It is not so easy to do skin tests with a needle or a knife on a baby, as the baby struggles, he has to be held down with one hand, and it is very difficult to make the scratches exactly the same depth and length and it is important to do so in order to read the tests accurately. This instrument is simply a small punch, like a leather punch, it is sharp on the end and makes a circular scratch.

I have derived a great deal of pleasure and profit from reading Dr Moro's book on Eczema. It is a masterly exposition of the subject but, as Dr Schick said, it is very interesting to see how little attention the Germans have paid to allergy and skin testing. Dr Moro in the preface of his book says he did not attach much importance to skin testing until he had written about half the book, he then decided to try them and see whether they were worth while and he became most enthusiastic about the allergic theory of eczema.

He believes sensitization to egg in utero is the primary step in the development of a great many infantile eczemas. The child being stamped as an allergic individual, the allergy may branch out in a number of different directions and he may become sensitized to a great many other things as well and have a multiple sensitization. Why some infants become sensitized and some do not is obscure; it may depend upon hereditary factors, or possibly on quantitative differences in the allergen ingested. This is a very attractive theory and fits in well with the facts of eczema as we observe them.

Another interesting thing about egg white, Woringer who writes so well on allergy believes there are two kinds of egg sensitive babies, one in whom there is simply skin sensitivity and no antibodies in the blood the other in whom there is skin sensitivity plus antibodies in the blood. He believes an eczematous child can not be cured by removing egg from the diet even if he is sensitized to egg and I am rather inclined to agree. I have seen innumerable older children sensitive to egg with positive skin tests, but I have never seen one cured by removing egg from the diet. He also believes eczema cannot be made worse by feeding egg. He looks upon infantile eczema as being not exactly an allergic phenomenon but a para allergic phenomenon going along with allergy, the whole substratum of the process being sensitivity to egg white or egg yolk with of course in some cases, primary sensitivity to milk, wheat or any other allergen as the case may be.

Dermatology at present is dominated very much by Bruno Bloch of Zurich and his ideas of eczema. Under his influence the German school confines itself to calling eczema an external dermatitis. A poison ivy or any other external dermatitis is eczema and nothing else is. A good deal of confusion has arisen on that account because in this country the dermatologists have a much broader definition of eczema. The followers of Bloch look upon adult eczema as a contact dermatitis and they determine sensitivity by means of the patch test.

I believe in certain infants we do get sensitivity to external things. I have had patients sensitive to wool silk cat fur dog hair or what not, but I believe the vast majority of reactions come from the ingestion. There are no metabolic changes particularly characteristic of infantile eczema. All metabolic researches have developed nothing of any great moment.

With regard to the use of milk free diets, Stewart and I some years ago developed Sobee, made of soy bean flour and olive oil etc. because it seemed we never would be able to tell exactly what rôle milk played in the development of infantile eczema until we could have a satisfactory diet without milk for the baby. I have fed a great many infants on this food and I believe one must not expect too much of it. It is not a cure-all for eczema by any means. If the eczema is due to milk sensitivity it will undoubtedly be cured by Sobee feeding provided there are not a great many other sensitivities. If the baby is sensitive to egg and milk and a number of other things, he is not very likely to do well with Sobee feeding. If the eczema is purely and primarily a milk case the results are very satisfactory. When we first prepared Sobee, we made it of barley flour and later with purified cornstarch on account of the objection Dr Bell has spoken of. All the Sobee for some time has been made with purified cornstarch and I believe before long arrow root starch will be used instead following the suggestion of someone in California.

Certain changes in the protein undoubtedly take place when milk is heated very hot. It is probably true that the lactalbumin is rendered less allergic by prolonged heating. The casein is changed very little. I am skeptical about "denatured" milks. I believe that in some cases of mild milk sensitivity, if the idiosyncrasy is due to lactalbumin alone, the heated milk may do very well but, on the other hand, if the idiosyncrasy is due to both casein and lactalbumin, as it frequently is, or to casein alone, heated milk will not do much and I believe a milk free diet is very much to be preferred.

I have been able to get very definitely positive skin tests with powdered milk heated to 130° C for one hour, just as large skin tests as I would with pure casein. I think the subject of heated milk deserves a closer and much more careful study than has been given it as we really know very little about what changes take place in casein when it is heated or indeed if any important changes do take place.

I have had very little experience with either specific or nonspecific desensitization because after studying the literature and talking with a good many people, I concluded it was probably not a very satisfactory procedure for private practice particularly. It takes a good many injections, there may be fairly severe reactions, results are pretty uncertain and if we do get an immunity, it lasts only a comparatively short time. I firmly believe we have no answer to infantile eczema until we have some method of rendering an allergic child nonallergic and that method will come some time in the future through some means of nonspecific therapy. If we have a child with eczema or asthma who has a multiple sensitivity as almost all of them have, it is absurd to expect to cure him by taking away all the things to which he is sensitive or to desensitize him specifically. Much of our treatment of infantile eczema is very crude and some of it rather silly, but I believe we will progress as time goes along.

DR. CHARLES SCHOTT (CHICAGO)—Dr. Schick, have you had any experience with the formic acid injections in eczema?

DR. SCHICK—We have no experience in eczema though we tried them in asthma. We had some cases which responded to it but we dropped it after a while because the results were not so encouraging.

DR. S. J. LEVIN (DETROIT)—I would like to ask about calcium therapy. I know a great many variable reports have appeared about the value of calcium in eczema and asthma. I have found that calcium given intravenously is of considerable benefit and is something we should give more attention to. In status asthmaticus, we hesitate to use adrenalin continuously because of the short duration of benefit but calcium gluconate or glucose calcium given intravenously in amounts up to 10 c.c. has been found to be very effective in controlling these cases, it has helped a great deal in infantile eczema. Whether there is some fundamental calcium imbalance in allergy I do not know. Perhaps there is some disproportion between the calcium and the phosphorus and by elevating the calcium portion, the normal relation between the calcium and phosphorus is obtained. I mention this as a useful practical point in therapy and handling these difficult cases which come in during the pollen season, or cases of status asthmaticus in which the ordinary methods do not seem to help.

Another point I wish to make is the relationship of the skin tests to severity of symptoms especially in cases of pollen asthma. We have found it does not seem to matter much whether positive skin tests are present in large degree, whether they are present only in small degree, or absent entirely. The amount of pollen extract to be given therapeutically is not related in the majority of the cases to the height of the skin reaction. A child with pollen asthma who gives no positive skin tests whatever but whose symptoms occur at the typical pollinating season for

ragweed may be extremely sensitive subcutaneously to the extract of pollen and very minute doses may have to be used. Just the reverse may be true of the patient with extremely large skin reactions.

In any of these pollen cases, the pollen count in the air must be considered. Some men use high amounts of pollen extract and others use very small amounts. One cannot state that a certain amount of pollen is sufficient to cure any case of pollen asthma or hay fever. We have a very high pollen count in Detroit. Kansas City has the highest pollen count in America and Buffalo and Chicago are next. The fourth position is occupied by Detroit. The same patient with the same sensitivity in an area with a low pollen count does not require many injections, but in the Detroit area we find we need tremendous doses of pollen extract almost to the point of obliterating the skin tests before we can obtain good relief. We give us a final dose from 1 to 2 c.c. of a 3 per cent solution which is a very strong solution for the average pollen case. On the other hand we see cases where we can obtain a dosage of only 0.05 c.c. of a 1 in 10,000 solution and still get relief. It is such an individual question and the therapy must be so very detailed and adjusted individually for each patient that I believe one should not make a general rule. Especially one should not depend too much on height of skin reactions in relation to the size of doses.

I also wanted to talk about the perennial treatment of pollen cases. Dr. Schick is rather opposed to the continuation of perennial therapy and perhaps it does have its disadvantages but, on the other hand, it offers to the patient a possibility of eventually stopping pollen injections. Vaughan of Virginia gives figures indicating 50 per cent cures after three years of continuous therapy. In my own experience perennial therapy produces what may be called a permanent cure in eighteen months. It is a development in the treatment of allergy which must not be discarded too readily.

The extract of pollen or of foods should not be looked upon as a toxic substance. Whether the reaction of the body against this substance is antitoxic as in the case of diphtheria toxin still has to be shown.

I have seen children subjected to series of elimination diets that produced a very bad constitutional effect with general damage to the child in loss of weight and resistance to disease in the hope that by chance, some food would be eliminated that might be causing the trouble. I believe we should not subject a child to such a serious method of diagnosis in the hope that by chance we will find the cause of their symptoms. It is far more accurate to do the skin tests first and avoid the possibility of injuring the child a general condition by a series of weird diets.

DR. SCHICK—The following theory about the effect of calcium can be evolved. I can remember from the basic experiment of Chiari and Jannuschke croton oil put in the conjunctiva of a rabbit's eye produces a tremendous inflammatory reaction. This reaction was suppressed by giving calcium previous to the instillation of croton oil. The linings between the endothelial cells are tightened and made less permeable for exudation. I tried the calcium treatment in many cases and the result was not striking. You can find very much in the literature of twenty years ago about calcium therapy as a preventive measure against hay fever. There is some possibility of influencing the intensity of secretion and of inflammatory reaction on the skin and mucous membrane, but we should not expect a real cure of the condition.

I agree with Dr. Hill that we should not put all the eczemas in one pot.

A hyperergic person is good soil for infections. Secondary infections complicating eczema must be considered. The eczema question is still not entirely solved, and we should be very cautious in our statements.

DR LEWIS WEBB HILL—I wish you would say some more about nonspecific therapy in eczema I know very little about it but feel quite strongly that is what we must have some time if we really want to deal with the disease satisfactorily This is beside the question of local treatment, of regulating the diet, and taking away something we think the child is sensitive to

DR SCHICK—If we find some causative agents then, of course, these should be taken away, but, I am sure there must be other ways of treatment If a child gets pneumonia or some other febrile disease, it is astonishing how quickly the eczema disappears and how different the skin looks within seventy two hours We do not know what goes on in the system, but we do know that in some way nature is able to make the eczematous reaction disappear

I have not had much personal experience with the nonspecific treatment and vaccine treatment in eczema I hesitate to apply this treatment because I feel we are going a little too far in injecting all these different substances

(Remarks by Dr Franklin J Corper, Chicago, not sent in)

DR SCHICK.—I wish to express my personal opinion about the perennial treatment It is possible that interrupted treatment eventually brings about a hyper sensitization and perennial treatment prevents it After interrupted treatment with tuberculin it happens that if one starts over again, one will find the patient more sensitive I repeat that skin reactivity and asthmatic conditions do not always go parallel Dr Peshkin showed me patients with pollen asthma who were absolutely negative to skin tests and still had typical pollen asthma He could only obtain a positive test by testing the conjunctiva with dry pollen powder There one sees the dissociation between the reaction of the skin and the reaction of the respiratory tract The skin is very sensitive and the respiratory tract not so much so There are also differences which may be explained partly by the different rate of absorption If a substance is injected subcutaneously, the absorption will be slow, when given into a vein, the absorption is so rapid that a very large amount of this offending substance enters the system at one time

(Remarks by Dr I. H. Tumpeo not sent in for publication)

DR. SCHICK.—It has been my experience that tetanus antitoxin is more toxic than many other therapeutic sera I have seen the worst kind of serum sickness after injections of tetanus antitoxin As the purification of tetanus antitoxin is as thorough as that of diphtheria antitoxin, I am unable to explain the difference on that basis I saw a child whom I had to keep under morphine for three days because of terrific joint pains There was nothing visible on the joints Other colleagues reported similar observations to me

We must differentiate between serum sickness starting after a normal incubation period and one starting after an abnormally short time If a child develops an intensive serum sickness eight to twelve days after injection, this has nothing to do with a previous sensitizing injection The whole discussion should deal with the accelerated and immediate reaction.

An important question is whether or not there is danger of an anaphylactic shock in children immunized against diphtheria by toxin antitoxin in case the child must be treated later with a therapeutic serum Such an occurrence is possible but extremely rare.

Another question I wish to discuss is the reaction observed in older tuberculous children and adults when toxoid (Anatoxin) is used for immunization against diphtheria The most satisfactory explanation is that tuberculous and other infections

change the general level of sensitivity to foreign protein so that the reaction is different from diphtheria toxin. Infants and children of preschool age show such reactions much less frequently.

We should not go so far as to name everything allergic this would lead to confusion. I am wondering whether we have the right to explain sudden death in eczema or hyperpyrexia on the basis of hyperergy. The mechanism may be a quite different one and we should look for other explanations.

No child of three or four years will be absolutely free from allergic features. Such features are usually mild, so that they have no special importance. There are different grades of reactivity in different individuals from mild to hyperergic reactions. Hyperergic reactivity has great clinical importance.

DR. MOORE.—I would like to inquire whether there has been a study of defects in the endocrine system of the allergic children. Barber has recently discussed the feeding of glands of internal secretion to certain types of children, the colicky child, the vomiter and I believe to the eczematous child. Has there been any work done on defects of the adrenal as a causative factor?

DR. L. W. HILL.—Would it be possible to settle the question of the danger of anaphylactic shock by looking for precipitins to horse serum in the blood?

DR. SCHICK.—I do not think so. We had the greatest difficulty in finding precipitins in the blood. The human being is a very poor producer of precipitin.

Academy News

The following have been appointed for the Nominating Committee

Chairman.—Dr Samuel McC. Hamill Philadelphia Pennsylvania

Dr E B Shaw, San Francisco California

Dr Hugh Lealle Moore Dallas, Texas

Dr Sterling H. Ashmun, of Dayton Ohio has been appointed a member of the Ohio State Committee.

News and Notes

International Pediatric Congress*

The third International Pediatric Congress, held in London on July 20-22, under the presidency of Dr G F Still, was attended by nearly 400 delegates from thirty countries. The inaugural ceremony took place in the Great Hall of the British Medical Association House, when T.R.H. the Duke and Duchess of York attended to open the congress and to welcome the members. H.R.H. the Duke of York, in expressing his pleasure at greeting so large a gathering, especially in view of the fact that this was the first international meeting in this country of physicians dealing with the diseases of childhood, made a few well chosen remarks, stressing the importance of pediatrics particularly on the preventive side. "Speaking as a father," he voiced the gratitude of parents far and wide who would benefit from the deliberations of the congress. The President and Sir Thomas Barlow expressed the thanks of the members to the Duke and Duchess for their interest in the congress and after the departure of the Royal visitors, the scientific proceedings began.

The first main discussion took place on the subject of the nature of allergy and its rôle in diseases of children. Dr Arnold Rich (Baltimore) spoke from the pathologic side and brought forward the results of experiments which demonstrated that in bacterial allergy the individual tissue cells are hypersensitive to the bacterial antigen and the allergic reaction is not dependent upon circulating antibody. He stressed that all recent work went to show that allergy is not essential for immunity. Experiments show that immunity can be separated from allergy and that neither of the two primary characteristics of immunity—the prevention of spread of bacteria and their efficient destruction—is dependent upon allergic inflammation for successful operation. He further pointed out that allergy, once established without immunity and acting alone, it lowers resistance to infection. Professor F Hamburger (Vienna) dealt more with the clinical aspects of allergy, basing his remarks mainly upon the study of problems of tuberculosis by means of the tuberculin reactions. Allergy could be shown to develop prior to the onset of the disease. It was continuous but subject to the fluctuations caused by other diseases—by light, food and other so far unknown factors, and such fluctuations might be the cause of exacerbations. In his opinion, the tuberculin reaction was of great value in prognosis and tuberculin should be used to a greater extent for prophylaxis. Dr Pehu (Lyons), in a paper prepared jointly with Dr P Woringer (Strasbourg), described the clinical aspects of the allergic states of nonbacterial origin, enumerating the various substances capable of sensitizing the human organism under the main headings of inhalation, food, drug and contact allergens. He proceeded to give a description of the clinical manifestations of the nonbacterial allergic states in the various systems affected, pointing out how the different allergens tended to affect different systems at various periods of life. He thought there were three possible causes of nonbacterial allergy: sensitization after birth, sensitization in utero, and hereditary transmission by the germ cells, the last being of a specific nature or merely the inheritance of a predisposition. Dr W R F Collins (Dublin) advanced the view that the same disease syndrome could be pro-

*British Med J July 29 1933

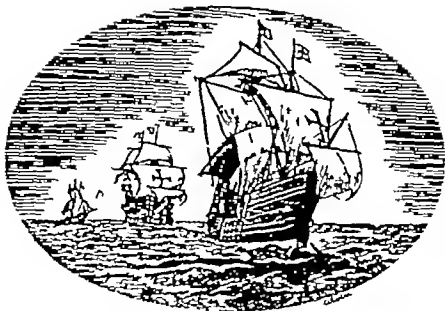
doed by more than one organism provided that the body was in the state of allergy, and he instanced erythema nodosum in this connection. Dr H. Ernberg (Stockholm) also discussed allergy in relation to erythema nodosum. Professor F. Groer (Lwow) stressed the kioetic aspects of allergy, dependent upon two main factors—the susceptibility of the body and the power to react on the part of the body. He explained how these factors could be assessed accurately in the case of a disease such as tuberculosis. Professor G. de Toni (Bologna), Professor R. Debré (Paris) and Dr B. Ratoer (New York) also took part in the discussion.

The discussion of the second day on the prophylaxis of milk-borne diseases was opened by Professor A. Pettersson (Stockholm) who dealt especially with the problem of tuberculosis. Not only was there the universal danger of bovine tuberculosis but in the speaker's opinion human tubercle were frequently introduced into the human body with milk. He also mentioned the risk of infection with the organisms of oedulant fever in those districts where infectious abortion occurred, but children under ten years of age fortunately appear to be either insusceptible or very slightly susceptible. Professor G. Bessau (Berlin) spoke of the saprophytic organisms in milk and their significance. The introduction of varieties of the colic bacillus by milk into the alimentary canal in children produced a completely different type of intestinal flora from that in the breast-fed baby, for example, and many of the digestive disturbances in the artificially fed baby could be attributed to the spread of *Bacillus coli* to the upper parts of the alimentary tract. In contrast to the adult, where the presence of the coli bacilli in the bowel had no deleterious effects, young babies might develop inflammation of the whole of the intestine, small and large, from this cause. Professor G. B. Allaria (Turin) explained that in Italy at present there was a strong movement for the improvement of the dairy industry and in the meanwhile it was of importance to seek an answer to the question of whether the advantages of giving raw milk as a 'live' liquid and attempting to prevent bacterial contamination were greater than those obtained by giving a sterile milk at the expense of its vital properties. The speaker thought that the importance of the vital properties had been exaggerated and that in the present state of the dairy industry in the majority of countries, the only course was to purify the milk by some thermic process. Professor P. Larchoulet (Paris) brought forward a survey of the possibilities of diminishing the risks from cow's milk by a thoroughly planned hygienic scheme by legislation and by municipal and collective measures. He summarized the position in certain countries and stressed especially the difficulties, concluded strongly in favor of pasteurization of milk under proper control as the ideal measure. Failing a proper organization, he thought the boiling of milk prior to consumption was the only course. Dr J. M. Hamill (London), gave a short review of the position in this country as regards bovine tuberculous infection in children. Since, as he pointed out, even certified and tuberculin-tested milk occasionally contained tubercle bacilli, there was no alternative to some treatment of the milk to destroy organisms. This he thought, was to be found in efficiently controlled pasteurization. He emphatically condemned the idea that the drinking of infected milk was valuable to produce an immunity. The discussion was continued by Professor F. Feer (Zurich), Professor S. Moorad (Copenhagen), Professor P. Rohmer (Strasbourg), Professor G. Frontali (Podua), Dr H. Bock (Berlin), Dr W. O. Davison (U.S.A.), Dr H. P. Wright (Montreal), Dr J. Duzar (Pecs), Professor G. Mouriquand (Lyons), Professor G. Neeggerrath (Freiburg), Dr W. Spolverini (Rome), Professor W. I. Jundell (Stockholm) and Dr G. Petranci (Hungary).

The afternoon sessions on the first two days and the morning session on the last day were devoted to short communications given in sectional meetings. On the social side the delegates were offered an excellent series of gatherings. On Thursday

Seriously, one comes to wonder at times just how many of the things that we have introduced into the child's life are real necessities, or actual improvements over the good old ways, and one might well ask oneself just how much chance there is, in the family that can afford all the frills, for the child to have what might be called a natural development. Or are our children really better for having the years once given over to irresponsible play all cut to pattern?

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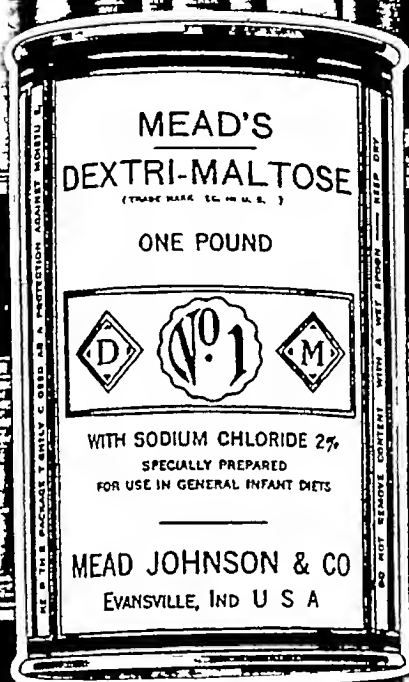
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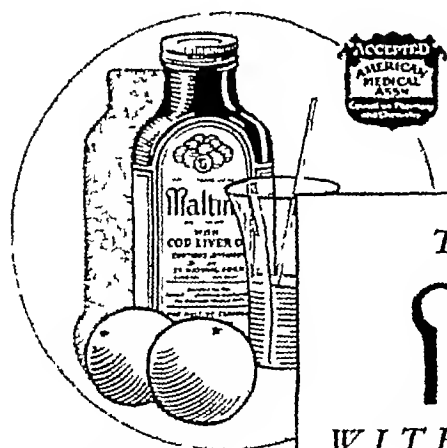
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A Specific for Rickets

Mead's Viosterol, on the other hand is capable of terminating the ricketic process in a brief period in virtually every type of case. Thus if given as a prophylactic in requisite dosage it may be expected to prevent not only bowing of the legs but also the more insidious skeletal defects such as malformation of the chest, hypoplastic teeth, and pelvic abnormalities, which may develop unnoticed when less effective vitamin D products are administered.

Especially Indicated for Prematures

Prematures, twins, infants of low birth-weight, and rapidly-growing, full-term infants are especially susceptible to ricketic deformities because of their greater need for calcium and phosphorus. Yet the first three types of infants, due to their small digestive organs, are generally unable to take even the usual dose of cod liver oil, much less increased doses. For them Mead's Viosterol is specific in preventing malformations just as it is in all other types of rickets.



Because of its potency Mead's Viosterol prevents and cures rickets, in small dosage without gastric upset quickly before deformity sets in.

Specify MEAD'S

MEAD JOHNSON & CO., Evansville, Ind., *Pioneers in Vitamin Research*

Please enclose proper postal card when requesting samples of Mead Johnson products to cooperate in preventing their research against malnutrition.



If this tired, worried, over worked mother were using Pablum for her babies' cereal feedings, she could have slept that extra much-needed hour instead of losing her temper while her children clamor for breakfast. For she can prepare Pablum in an instant, directly in the cereal bowl, simply by adding water or milk of any temperature—salt, cream and sugar for the older child and herself.

GETTING up an hour earlier in the morning is an inconvenience for most persons but for the mother of young babies it is a hardship sometimes almost tragic, frequently nullifying the best planned pediatric advice.

This is especially true in the case of the nursing mother whose supply and quality of breast milk are affected by emotional shocks resulting often in agalactia and sometimes giving rise in the baby to diarrhea, colic and even convulsions. Furthermore the mother's emotional stress brings about a train of behavior on her part which is reflected in the child's psychologic reactions so that a vicious circle of bad habit formation is set up.

From this angle, the recent introduction of the pre-cooked form of Mead's Cereal known as Pablum assumes new

importance in the doctor's psychological handling of both mother and child quite aside from its nutritional value.*

Because Pablum can be prepared in a minute, the mother can sleep the extra hour she would otherwise be compelled to spend in a hot kitchen cooking cereal. Added rest means better poise so that petty annoyances do not bring jaded nerves. Prompt feedings prevent many childhood tantrums, and a satisfied baby usually eats better and enjoys better digestion and growth.

*Like Mead's Cereal Pablum represents a great advance among cereals in that it is richer in a wider variety of minerals (chiefly calcium, phosphorus, iron, and copper) contains vitamins A, B, E and G is basic forming and is non-irritating. Added to these special features, it is adequate in protein, fat, carbohydrates, and calories. Pablum consists of wheatmeal, oat meal, cornmeal, wheat embryo, yeast, alfalfa leaf and beef bone.

MEAD JOHNSON & CO., Evansville, Indiana, U S A

"...Viosterol given in adequate antirachitic for curative

There are now available a considerable number of valuable, indeed almost specific, agents for the prevention of rickets

Whether one or the other should be adopted will depend not so much on their efficacy in preventing rickets as on their availability their cost to the consumer, their palatability, and other non medical considerations conclude Drs Hess and Lewis after extensive work in comparing clinical results with various sources of Vitamin D

For prophylaxis, many products have been found satisfactory as a routine, cod liver oil, both regular and fortified with Viosterol, Viosterol in Oil 250 D, halibut liver oil, and irradiated milk. Any of these anti rachitics given in adequate dosage, will effectively protect infants against rickets

For therapy, however, a distinction should be made between the various measures available

High potency is not only desirable. It is essential. The quicker healing can be produced, the less risk of the baby developing permanent deformities

The agent selected should offer maximum potency *at the least cost*. It should be readily available for every baby. It should be absolutely stable and palatable

From all of these angles—effectiveness, cost, availability, dependable results and palatability—Viosterol in Oil 250 D becomes a therapeutic agent of choice!

Drs Hess and Lewis call it *the most satisfactory*

factory anti rachitic for curative purposes!

Physicians! Note these advantages of Viosterol!

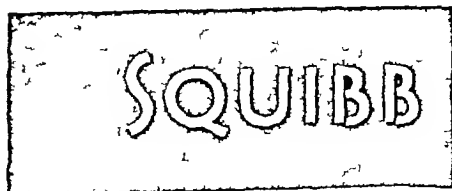
Its high potency—No other agent supplies more Vitamin D. Each drop contains 75 units. This is 250 times as much as the standard cod liver oil defined by the Wisconsin Alumni Research Foundation

Its cost—Because Viosterol supplies Vitamin D alone, it is less expensive to use than other preparations which supply additional factors. Mothers will find it an economy

Its palatability—Viosterol does not cause digestive disturbances. It is well tolerated by the very youngest infants

Its convenience—Dosage is by the drop and easily administered

Prescribe Squibb's for dependable results! The potency of Squibb's Viosterol in Oil-250 D is uniform and unchanging. Squibb uses a special method in preparing it. By making the solution from a purified vegetable oil, charging it with carbon dioxide, and packaging it under air tight conditions, the high vitamin content is protected against deterioration. Always be sure of the Viosterol you prescribe. Specify *Squibb's!*



dosage is the most satisfactory purposes"

HESS A. F. LEWIS J. M. J. A. M. A. 181 184 (JULY 15) 1933

Squibb Viosterol In Oil 250 D
Economical effective convenient An
agent of choice for the healing of rickets



VIOSTEROL
IN OIL 250 D



MELLIN'S FOOD—MORE THAN A CARBOHYDRATE

The main purpose of all milk modifiers is the same—to provide carbohydrates in adequate amount as a part of the infant's diet.

Mellin's Food is a carbohydrate—and more.

It contains 58.88% maltose and 0.69% dextrins.

It contains 10.35% protein, extracted from the wheat and barley which are its chief ingredients.

It contains 1.05% mineral salts derived from the whole grain.

It contains 3.25% potassium bicarbonate added during the process of manufacture. It tends to promote normal bowel action.

It has been favorably known the world over for more than half a century and its use is consistent with today's sound pediatric knowledge and practice.

Literature and Samples of Mellin's Food Gladly Supplied—to Physicians Only
MELLIN'S FOOD COMPANY, Boston Mass

ALBOMALT

the
really honest
REGULATOR



A jelly form emulsion of
the finest mineral oil ob-
tainable with the finest
malt of high diastatic
quality

Try it in your practise, especially on the "little
patients" and their mothers

Send for trial jar and literature Just mail the
coupon

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Quality Guaranteed

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BRIDGEPORT, CONN

JP 10

Please send literature and trial jar of ALBOMALT

M.D

St. & No.

City & State



how about my teeth?

GUARD THEM WITH A TOOTH-PROTECTING DIET

Dental decay is the most nearly universal malady from which the human race suffers. How important it is to start children out with strong, sound teeth—if for no other reason than to protect the health of the rest of their bodies.

Research has shown that dental caries was greatly reduced simply through the addition of vitamin-D to the diet. Now that vitamin-D is available in such a convenient, wholesome form through Bond Bread, there is no longer any excuse for depriving children of this protective element. Best of all, the vitamin-D in Bond Bread costs the public absolutely nothing.

You are absolutely safe in recommending Bond Bread as a source of vitamin-D. For one thing, the claim that Bond Bread is a *rich source* of vitamin-D is accepted by the Committee on Foods of the American Medical Association. For another, the vitamin-D is added under the most painstaking scientific control, and the bread is periodically subjected to biological assays by independent research laboratories. Never is the vitamin-D content less than the equivalent of two teaspoons of Steenbock Standard Cod Liver Oil for each pound of bread.

Why not try this delicious bread yourself tomorrow? Watch the effect on your own oral health over a period of months. The improvement will naturally prove to you more convincingly than words the wisdom of recommending its use generally.

Experiments Now in Progress Prove Need for More Vitamin-D*

In four institutions for children, caries was greatly reduced simply by adding vitamin-D to the normal diet. The children were already receiving what is generally considered an adequate diet, even including the ordinary supply of vitamin-D and sunshine—but those who got no extra vitamin D had *three times* as many cavities! The dentists making the examinations were completely impartial. They did not even know which children had received the extra vitamin D.

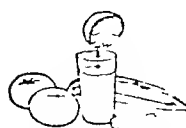
The prevalence of rickets among children is evidence of the need for extra vitamin D. Caries in adults is a sign of the continuing need of additional vitamin D in later life.

* Name of research organization on request

Address Dr. J. G. Coffin
Technical Director GENERAL
AL BAKING CO. 420 Lexington
Avenue N. Y. City

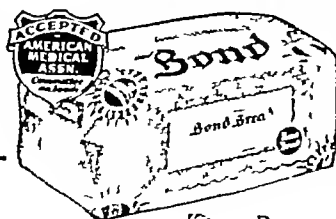
Bond Bread

Also Bond Bakers Wheat Bread
Rich sources of vitamin-D



Vitamins A and C

+



Vitamin-D

+



Calcium
and Phosphorus

=



Sound Teeth

SMA The Only Antirachitic Breast Milk Adaptation

SO SIMPLE

that even Mrs

--- -- --- *can prepare it properly

SO SIMPLE

that Mrs -- -- --
much worry and trouble

†will thank you for sparing her

(† No doubt you can supply names from your practice)

ANYONE CAN FOLLOW THESE SIMPLE INSTRUCTIONS



To each
measure of
S. M. A.

+

One ounce
of boiled
water

= One fluid ounce
of S. M. A.
ready to feed.

This proportion remains unchanged. As the infant grows older you merely increase the quantity as with breast milk. (See table below)

SAVES PHYSICIAN'S TIME TOO

S. M. A. is simple to prescribe. The physician is relieved of exacting detail because he has only to increase the *amount* of S. M. A. (as with breast milk) when in his judgment it becomes necessary. The accompanying chart suggests average amounts.

The physician's time is also saved because the chances are good for excellent results under his skilled supervision.

SUGGESTED FEEDING TABLE

Infant	Total Quantity In 24 Hours In Ounces	No. of Feedings	Quantity per Feeding In Ounces
2 days	1 to 2½	2 to 5	½ to 1
3 days	2½ to 5	3 to 4	½ to 1½
4 days	5 to 7½	4 to 5	1 to 1½
5 days	7½ to 10	5 to 7	1 to 2
6 days	10 to 12½	5 to 7	1½ to 2½
7 days	12½ to 15	5 to 7	2 to 3
2 weeks	15 to 17½	5 to 7	2 to 3½
4 weeks	17½ to 20	5 to 7	2½ to 4
6 weeks	20 to 22½	5 to 7	3 to 4½
1 month	22½ to 25	5 to 6	3½ to 5
2½ months	25 to 27½	5 to 6	4 to 3½
3 months	27½ to 30	5	5½ to 6
3½ months	30 to 32½	5	6 to 6½
4 months	32½ to 35	5	6½ to 7
5 months	35 to 37½	5	6½ to 7½
6 months	37½ to 40	5 to 4	6½ to 10

6 to 7 mos. At this age it is customary to add soups and vegetables to the diet especially spinach.

* These quantities refer to fluid ounces of S. M. A. diluted according to directions.

TIME SCHEDULE

7 feedings: 6 9 12 5 6 9 and once during night.
6 feedings: 6 9 12 3 6 and 9 or later
6 feedings: 6 10 2 6 10 and 2
5 feedings: 6 10 2 6 and 10 or later
5 feedings: 6 9 12 3 6 and 9 or later

NUMBER OF FEEDINGS IN 24 HOURS

The number of feedings in 24 hours should likewise be the same as those allowed breast-fed infants, generally stated not more than seven and not less than five. However, when the infant reaches the age of 6 to 7 months it is customary to replace one of the feedings with an 8 ounce meal of farina broth soup.

S. M. A RESEMBLES BREAST MILK

S. M. A. is a food for infants—derived from tuberculin tested cows milk, the fat of which is replaced by animal and vegetable fats including biologically tested cod liver oil with the addition of milk sugar potassium chloride, and salt altogether forming an *antirachitic food*. When diluted according to directions it is *essentially similar to human milk* in percentages of protein fat, carbohydrates and ash, in chemical constants of the fat and in physical properties.

ETHICAL OF COURSE

If babies were all alike, it might not be quite so necessary to have a physician plan and supervise feedings. However from the very beginning every package of S. M. A. has carried these instructions prominently on the label. *Use only on order and under supervision of a licensed physician. He will give you instructions.*

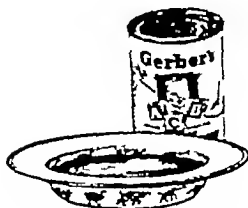


S. M. A. CORPORATION
CLEVELAND OHIO

S. M. A. PRODUCES RESULTS MORE SIMPLY, MORE QUICKLY



There's more than JUICE IN A TOMATO!



THIS PLUMP TOMATO is bursting with a cargo of nutrients that infants need. But—infants can not be fed raw tomato, because of the irritating, indigestible skin and seeds. The only way, until comparatively recently, to get rid of the skin and seeds has been to extract the juice and throw away the rest.

PRACTICALLY EQUAL to orange juice in Vitamin C value, tomato juice has long played a part of recognized importance in the infant dietary. Its ready availability has commended it to physicians and mothers alike. Here, then, is a glass of tomato juice—very good for babies. But—there is more than juice in a tomato!

WHEN THE JUICE is extracted, more is left behind than skin and seeds. *Rich tomato solids are lost.* These solids contain vitamins (A, B, and C) and essential minerals.

In *Gerber's Strained Tomatoes, these valuable elements are *saved*. Only the skin and seeds are removed from choice tomatoes, leaving the solids in a finely subdivided and readily acceptable form. Nutritive values are conserved by the Gerber vitamin-retaining process.

*A FOOD— NOT A BEVERAGE

Gerber's Strained Tomatoes are twice as concentrated as canned tomatoes or tomato juice. Sterile water may be added to give the desired dilution. A REQUEST: If you have occasion to prescribe this product, please do not refer to it as Gerber's Tomato Juice, as this may confuse the mother. Gerber does not produce a tomato juice for infants. There is more than juice in a tomato.

Strained Tomatoes Green Beans Beets Vegetable Soup Carrots Prunes Peas Spinach
4½-oz. cans Strained Cereal 10¼-oz. cans 15c

Gerber's

9 Strained Foods for Baby

GERBER PRODUCTS COMPANY Fremont Mich.
(In Canada: Fine Foods of Canada, Ltd., Windsor Ont.)

Please send me ☐ Reprint of the article "The Nutritive Value of Strained Vegetables in Infant Feeding"

☐ Sample can of Gerber's Strained Tomatoes

Name _____

Address _____

City _____

State _____



JP 10



Announcing CAPSULES OF SMACO CARITOL

IN response to demand by physicians small Caritol capsules are now available in packages containing 25 and 50 each, identified as Smaco 500. Each capsule represents 5 drops of Caritol (0.3% carotene in oil). The liquid form of course, is still available (Smaco 505).

Caritol capsules provide an easy way to measure doses and are especially recommended for individuals who object to drops.

FRUIT AND VEGETABLE FORM OF VITAMIN A - NO FISHY TASTE

Carotene is derived from fresh vegetables and thereby represents the form in which most vitamin A is consumed by the human body.

HELPS BUILD RESISTANCE

Caritol by virtue of its vitamin A activity promotes growth and, as indicated by experimental studies, may be an aid toward the establishment of resistance of the body to infections in general.

ALSO CAPSULES OF CARITOL WITH VITAMIN D

For patients who object to Cod Liver Oil we offer capsules of Caritol with Vitamin D (Smaco 520). The vitamin D is prepared for therapeutic use by methods (Zucker process) developed at Columbia University. These small capsules are offered in boxes of 25. Each capsule is equivalent to 5 drops of the liquid form. Therefore two capsules are equivalent to three teaspoons of good cod liver oil plus any advantages that may be attributed to Carotene itself.

Prescribe capsules of Caritol, plain, or with Vitamin D to help build resistance. *Easy doses, no fishy taste no bad after-taste.*

S M A CORPORATION
CLEVELAND, OHIO



Information about Karo Syrup

Which Will Interest All Physicians —

Particularly Pediatricists

In response to numerous requests from physicians, Corn Products Refining Company is pleased to publish the following analytical data about Karo Syrup (Blue Label)—which has proved so effective in the feeding of infants

The following acceptance of Karo (Blue Label) by the committee on foods, appeared in Journal of the American Medical Association, January 23rd, 1932

The product is a mixture of corn syrup with a relatively small amount of refiners' syrup. The refiners' syrup must be acceptable in flavor and color and fulfill the U. S. Department of Agriculture standard for that product. "Refiners' Syrup, treacle, is the residual liquid product obtained in the process of refining raw sugars, and contains not more than 25 per cent of water and not more than 8 per cent of ash."

The corn syrup is manufactured by hydrolysis of high grade corn starch in

dilute hydrochloric acid suspension. The mixture is heated under steam pressure until chemical tests indicate the desired degree of hydrolysis. The resultant mixture is almost completely neutralized with sodium bicarbonate and filtered through white linen filter cloth, the filtrate is passed through a deep bed of animal charcoal for decolorization and deodorization. The final filtrate, which is water clear and odorless, is concentrated under reduced pressure to a density of 1.38 (20 C / 20 C).

CHEMICAL COMPOSITION

	per cent
Moisture	25.3
Ash	0.6
Fat (ether extract)	0.0
Protein (N X 6.25)	0.2
Dextrins (by difference)	37.1
Maltose (method of Wesener and Teller J. Indus. & Engin. Chem. 1: 1009 1916)	22.2
Dextrose (method of Wesener and Teller J. Indus. & Engin. Chem. 1: 1009 1916)	7.5
Sucrose	4.8
Invert Sugar	2.3
Titratable acidity as HCl	0.05

CORN PRODUCTS REFINING CO.
17 Battery Place New York





RAPIDLY GAINING FAVOR

ALERDEX - THE PROTEIN-FREE
MALTOSE AND DEXTRINS

WHY IS ALERDEX PROTEIN-FREE?

• Since certain proteins are frequently the cause of eczemas and other forms of allergy it is desirable to eliminate these offending proteins from the infant diet. Cereal proteins are frequently present as contaminants in some milk modifiers. The routine use of a protein free carbohydrate in all milk modifications should help to diminish the incidence of these troublesome eczemas. Alerdex is a protein free carbohydrate developed by our Research Division to meet this need and the demand for it is steadily increasing.

A modest announcement of Alerdex a year ago found physicians ready and anxious for such a product. There is now a definite trend to use Alerdex routinely in all milk formulas.

Of course Alerdex should always be used as the carbohydrate addition with Smaco Hypo Allergic Milks with the assurance that eczemas due to cereal protein sensitization will not be aggravated.

CHARACTERISTICS OF ALERDEX

1. Helps prevent eczemas when used routinely due to absence of offending protein.
2. Use present formulas because Alerdex has same caloric value and percentage of maltose and dextrins.
3. Does not cake on exposure to air because it is non hygroscopic.
4. Dissolves readily in warm water or milk.
5. Snow white, free flowing powder
6. Inexpensive—in spite of extra processing under technical control, costs no more.

APPROXIMATE ANALYSIS OF ALERDEX

Alerdex is essentially a mixture of approximately equal parts of maltose and dextrin. It is prepared by a new thermally-controlled process of the enzymic hydrolysis of non cereal starch as a result of which it contains no protein contaminant.

Moisture	3.0
Ash	0.3
Fat (ether extract)	0.0
Hydrolyzed protein (N x 6.25)	0.05
Reducing sugars as maltose	50.0
Dextrin (by difference)	46.0
Levelt teaspoons per ounce	4
Calories per levelt teaspoon	27½
Calories per ounce	110



Prescribe Alerdex in your own practice. For samples and literature simply attach this paragraph to your letterhead or prescription blank. S.M.A. Corporation 4414 Prospect Avenue, Cleveland, Ohio 60-103

© 1952, S.M.A. Corporation, Cleveland, Ohio

PRESCRIBE ALERDEX THE PROTEIN-FREE MALTOSE AND DEXTRINS

Double Rich IN VITAMIN "B"

Ralston Wheat Cereal provides all the food value of finest whole wheat (only coarsest bran removed).

PLUS added quantities of pure wheat germ, which make it richer than any other cereal in the anti-neuritic, appetite-stimulating vitamin B.



It is a temptingly delicious, satisfying food, equally popular with children and adults.

It cooks in five minutes—costs less than one cent a serving.

Mail the coupon for Research Report on the New Ralston Wheat Cereal and samples for testing.

RALSTON PURINA COMPANY, Dept. I
149 Checkerboard Square, St. Louis, Mo

Please send me copy of your Research Report on the new Ralston Wheat Cereal and samples for testing

Name

Address

This offer limited to residents of the United States



ALLERGIC MANIFESTATIONS AND HYPO-ALLERGIC WHOLE MILK



Allergic manifestations caused by food may take any of the following forms

- ECZEMA, especially in infants, caused by ordinary milk.
- GASTRO ENTERIC DISTURBANCES, as vomiting diarrhea constipation
- HYPERACUTE TYPE, with urticaria asthma and symptoms of shock.
- BRONCHIAL ASTHMA.
- URTICARIA.
- ANGIONEUROTIC EDEMA.
- ERYTHEMA MULTIFORME

Where milk protein is responsible for such disturbances physicians have reported excellent results from the use of Smaco Hypo-Allergic Whole Milk, prepared from tuberculin tested cows' milk which is given thermal treatment equivalent to refluxing.

Smaco Hypo-Allergic Whole Milk is well tolerated in many cases and can be used in definitely as the processing does not remove any essential food element from the milk; the constituent amino acids are still present in the same proportions as before.

The milk thus rendered less allergic is then spray-dried in special equipment and packed in one pound containers in an atmosphere of inert gas (nitrogen). The cost of the powder is 25% less than the liquid form.

CHARACTERISTICS of Powdered Hypo-Allergic Whole Milk (Smaco 302)

Helps prevent eczema in patients hypersensitive to milk protein.

Can be used indefinitely because all essential food elements of milk are still present.

Use present formulas since this is real cows' milk, not a substitute.

Convenience Individual feedings may be made up for infants.

Lower cost Powder form costs 25% less than liquid.

Spray dried in equipment reserved for Hypo-Allergic Milk and Alerdex.

It keeps. Hermetically sealed in an atmosphere of inert gas (nitrogen) to prevent deterioration.

Developed by the
Research Division
of S.M.A. Corporation
Cleveland
Ohio © 1933

now in
**POWDERED
FORM**
MORE CONVENIENT
25% LOWER COST

A POPULAR PAMPHLET

This twenty-two page booklet has proven popular with the medical profession. It contains a brief resume of current literature on Milk Allergy, quoted by fifty-one authorities, prepared especially for Physicians. Send the coupon for a complimentary copy of the fifth edition.



S.M.A. CORPORATION

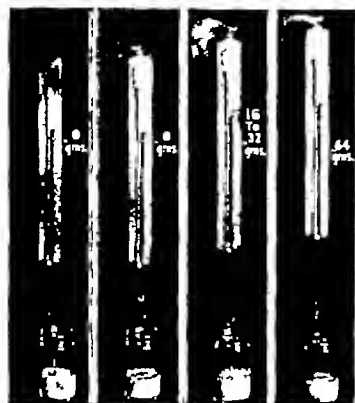
CLEVELAND, OHIO

□ Trial package Hypo-Allergic Whole Milk (powder) 56-103 □ Milk Allergy booklet with bibliography
(For samples and literature without obligation simply attach to prescription blank or letterhead.)

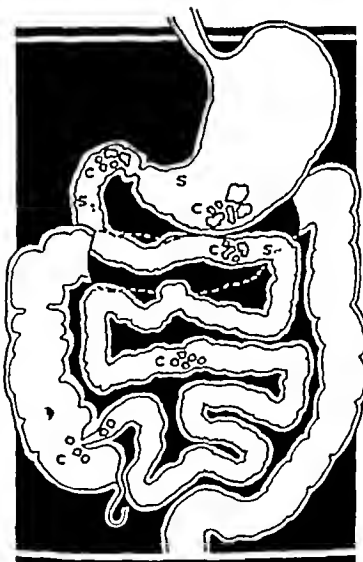
CURD TENSION

- AND INFANT FEEDING -

ITS · EFFECT · UPON · THE · ASSIMILATION · OF
FATS



BREAST MILK SIMILAC POWDERED MILK MILK COW'S MILK



C—Cow's milk S—Similac
Schematic drawing of the relative size of the curds of cow's milk and Similac vomited by six weeks old puppies after one half hour's ingestion

"**F**AT has a caloric value more than twice that of either carbohydrates or protein and serves very well to make up the necessary energy or caloric requirement. Two of the important vitamins, 'A' and 'D', are associated with the fat of milk and when the diet is low in milk fat these vitamins must be supplied in some other form"¹

"When milk curdles in the infant's stomach it entangles a large proportion of the milk fat in its meshes and only such fat as lies near the surface of the curd can be reached by the digestive juices. The amount of fat in the curd depends upon the amount of fat in the milk"²

The soft, fine curds of SIMILAC, which register zero on the tensiometer, expose a greater surface area for the digestion of the fat than do the large, tough curds of fresh cow's milk

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes. Result—a more complete utilization of the food elements

¹ Marriott Infant Nutrition, pg 49

² Talbot Morse and Talbot, Diseases of Nutrition and Infant feeding, pg 48

Samples and literature
will be sent on receipt of
your prescription blank

SIMILAC—Made from fresh skim milk (casein modified); with added lactose, salts, milk fat and vegetable and cod liver oils

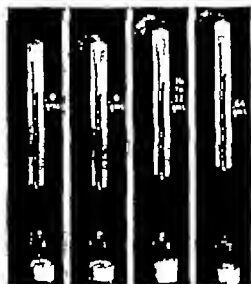


M & R
DIETETIC LABORATORIES, INC.,
COLUMBUS, OHIO.

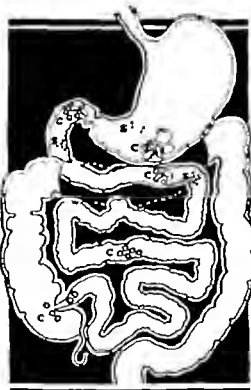
CURD TENSION

- AND INFANT FEEDING -

ITS EFFECT UPON THE ASSIMILATION OF CARBOHYDRATES



BREAST MILK SIMILAC POWDERED MILK COW'S MILK



C-Cow milk. S-Similac
Schematic drawing of the relative
size of the curds of cow milk and Similac vom-
ited by six weeks old puppies after one-
half hour ingestion.

THE curds of milk contain only a small amount of carbohydrates, sufficient, however to be a disturbing factor in infant feeding.

"A large part of the digestion and absorption of the carbohydrates takes place in the upper part of the small intestine."

"The disaccharides, maltose, sucrose and lactose, are converted into monosaccharides through the action of enzymes secreted by the small intestine and are absorbed in the form of monosaccharides."

"When absorption is impaired, some sugar may reach the large intestine and here be attacked by the bacteria present. Sugar itself rarely appears in the stool, it being decomposed to form acids and gases."

The large, tough curds of cow's milk are more slowly disintegrated and thus more slowly release the encased carbohydrates than the soft, flocculent curds of SIMILAC.

The disintegration of the curd of cow's milk may not be completed until after the curd, with the encased carbohydrate, has passed that portion of the small intestine where the enzymes for the conversion of disaccharides into monosaccharides are present. There is not this possibility when SIMILAC is fed because the fineness of the curd of SIMILAC does not permit of the encasement of carbohydrates to any extent.

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes. Result a more complete utilization of the food elements.

¹London & Polewsova: *Zeitschr f physiol. Chem.* 1946, XLIX, 222.
Marriott: *Infant Nutrition*, pg. 81.

Samples and literature
will be sent on receipt of
your prescription blank.

SIMILAC—Made from fresh skim milk
(casein modified); with added lactose salts,
milk fat and vegetable and cod liver oils



M & R
DIETETIC LABORATORIES, INC.,
COLUMBUS, OHIO.

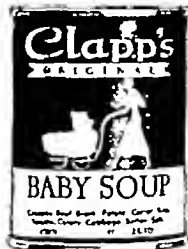
*"My doctor
knows what
I like!"*



IT'S probably no news to thousands of doctors—and others concerned with the care of infants—that babies *like* Clapp foods. Just watch a little tot eagerly attacking a Clapp meal and that point is definitely proved.

But perhaps some doctors do not know that Clapp's Original Baby Soups and Vegetables are now packed in the new Enamel Purity Pack. And that in this packing—the purest that foods can receive—every Clapp item is selling at a new *low* price of 15c a can!

Now you can put the infants in your care on this varied and nourishing diet, which is,



Clapp's Original Baby Soups and Vegetables...also packed in glass jars at former prices



at the same time, a real *economy* diet.

We want you to see and try Clapp foods in this modern new packing. Send in the coupon below and we'll forward to you—free of charge—America's largest variety of baby foods.

• 15 VARIETIES •

<i>Baby Soup (Strained)</i>	<i>Baby Soup (Un- strained)</i>
Vegetable Soup	Beef Broth
Wheatmeal Cereal	Spinach
Carrots	Peas
Tomatoes	Beets
Beans	Prune Pulp
Pulp	Apple Sauce
	Asparagus
	Wax
	Apricot



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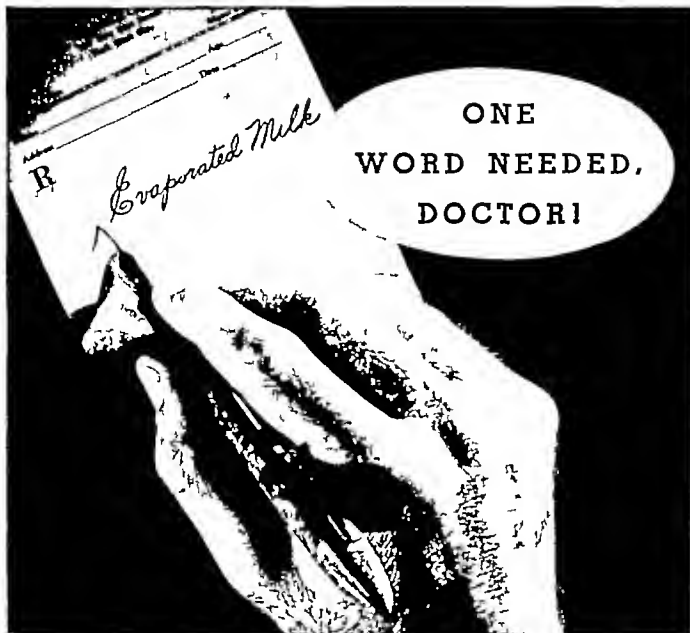
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Dr. Alfred I. Hess in the City of New York Department of Health Quarterly Bulletin, Vol. 1, No. 2, 1933 which states editorially, 'So many inquiries have come to the Department of Health regarding irradiated milk that we have asked Dr. Alfred I. Hess to prepare the following brief article on the subject for our readers.'

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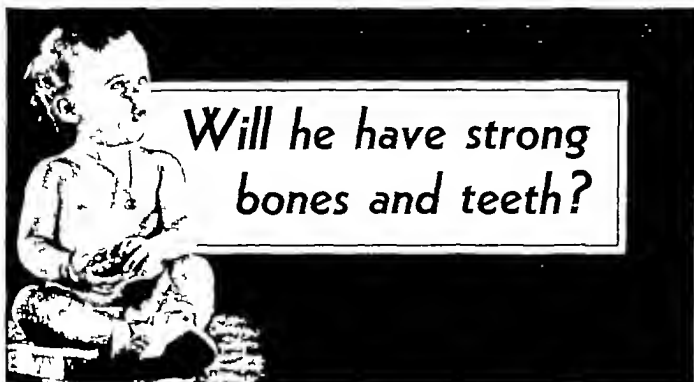
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GEORGE E. PERCY, M.D.
In American Medicine, July 1932

"In infantile eczema generalized exposures for tonic purposes exert pronounced benefit. In adults affected with eczema, ultraviolet therapy is applied for similar purposes and occasionally attains equally notable results, especially in eruptions of internal origin produced by derangements of the calcium metabolism."

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GEO. CLINTON ANDREWS, A.B., M.D.
Diseases of the Skin"
pp. 231 and 421 (1931)

"It (eczema) is not an external disease or an internal disease. It is both always, and at the same time, and often responds to radiation therapy when other remedies fail."

C. M. HENRY, M.D., C.M. F.A.C.S.
In Can. Med. Assn. Jour., Dec. 1931

"This constitutes about one-quarter of all skin diseases. So varied are these that it is impossible to lay down the treatment by ultraviolet radiation with any degree of precision. But when we consider that the underlying pathology of all of them namely either a deficient metabolism on the one hand or perverted or excess metabolism on the other — and actinotherapy at any rate temporarily alleviates the effects of disordered metabolism — it will be seen that there is sound foundation for its use in eczema."

F. H. HUMPHRIS, M.D.
In Artificial Sunlight and Its Therapeutic Uses (1929) p. 171

"In eczema I employ local ultraviolet in a dose sufficient to produce a strong erythema. Systemic ultraviolet follows, treatment being given on alternate days."

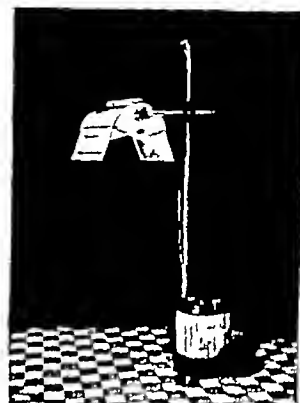
EDWIN L. LEBBERT, M.D.
In Physical Therapeutics Nov. 1929

"Ultraviolet radiation proves a very valuable therapeutic agent in this common condition especially in its subacute and chronic forms."

ELEANOR H. RUSSELL, M.D., and
W. KERR RUSSELL, M.D.
"Ultra Violet Radiation and Actinotherapy"—page 540 (1928)

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MRS. SCHULTZ, M.D.
In Arch. of Pediatrics, Oct., 1927



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Fat	2 1%
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Cal per oz.	18

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Carbohydrate	6 5%
Cal per oz.	20

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*"The Vitamins in Health and Disease" by Barnett Aure, Century Co., 1933.

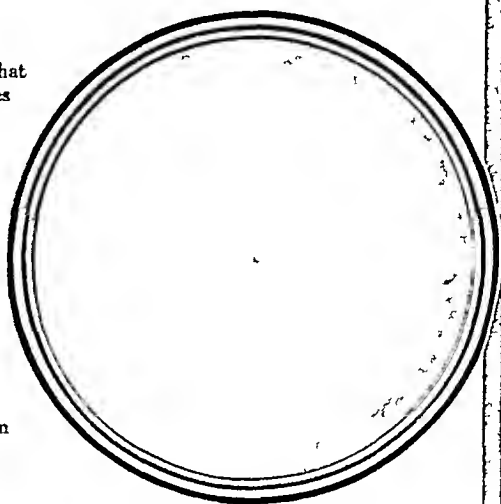
SQUIBB CHOCOLATE
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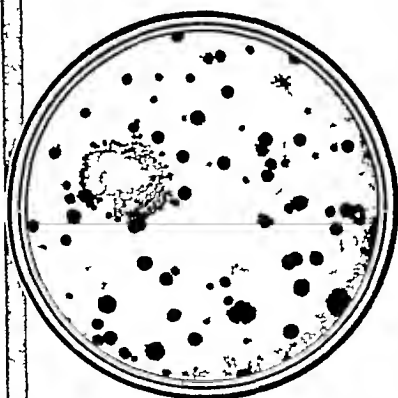
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The Journal of Pediatrics

VOL. III

OCTOBER, 1933

No 4

Original Communications

SIGNIFICANCE OF THE WATER METABOLISM IN HEALTH AND DISEASE

IRVINE McQUARRIE, M.D.
MINNEAPOLIS, MINNESOTA

INTRODUCTION

WERE we to decorate a map of the Western Hemisphere with pins representing the geographical distribution of individual contributors to the comparatively scanty literature on the topic of this evening's dissertation it so happens that your own city would be the most densely pegged center before us. Because of this fact, I feel twice honored in having been invited to give this year's Packard Memorial lecture on the subject of water metabolism.

Unfortunately the breadth of our subject will permit only the most superficial consideration of its many interesting phases. Certain sub-topics admittedly of the greatest interest and importance such as those relating to the mechanisms of edema formation and urinary secretions will purposely be given less attention here than they deserve because the readily available medical literature abounds in papers dealing with them. Whereas most treatises, dealing with the water exchanges of the body direct attention primarily to other aspects of the metabolism and only secondarily to water, it will be my intention to reverse this order in the present discourse, purely for the sake of emphasis.

Although the broad science of metabolism had its very beginning in the experimental studies of Sanctorius of Padua (1561-1636) on the

From the Department of Pediatrics, University of Minnesota, Minneapolis.
The Annual Frederick Packard Memorial Lecture. Presented before the Philadelphia Pediatric Society April 11, 1933.

"insensible perspiration," it is obvious to every one acquainted with the subject that progress in the field of water metabolism has lagged far behind that in other branches of physiology. The clinician has indeed long recognized the practical importance of water in certain disease states and has always credited it with a place among the essential constituents of the diet, but appreciation of its true significance in the body economy is only now beginning to manifest itself. That physiologists as a class have likewise failed in the past to give the problems of water metabolism their due recognition is evident from the fact that extensive investigations have not as yet been made with methods comparable to those which have so greatly advanced our knowledge regarding the intermediary metabolism of the proteins, fats, carbohydrates and minerals, and that concerning the vitamins and the total energy exchanges of the body.

Yet, if any single constituent of the living organism, or of the food which goes to maintain it, can be said to be the most important, water must be given that distinction, as attested not only by its quantitative position among the major constituents but also by the multiplicity of its essential physiologic rôles. Without water there can be no life, and for each organ there appears to be an optimal state of hydration for normal functioning. Whereas a mammal, such as the dog or man, may survive for a month or longer without all other food, losing practically his entire glycogen and fat stores and as much as half of his body protein, death may occur if he is deprived of water for longer than a few days, or when he has lost but little more than one-fifth of the water incorporated in his tissues. When it is remembered that the cells of the body are entirely dependent for their protection against the vicissitudes of the external world upon a delicately adjusted internal environment, characteristically watery in nature, the significance of the statement by Rubner that "the water content of the tissues is anxiously supervised by Nature," can be appreciated. As long ago as 1860 Claude Bernard, father of modern physiology, clearly expressed the importance of the fluid matrix when he said, "It is the fixity of the '*milieu intérieur*' which is the condition of free and independent life" and "all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment."¹ Cannon² quotes Haldane as saying, "No more pregnant sentence was ever framed by a physiologist." We might add, that no more accurate expression of what our ultimate objective in therapeutics should be is likely ever to be made, because homeostasis or constancy of the body processes and materials is synonymous with health. Water is the most important single agent in making such constancy possible.

THE CHEMICAL NATURE OF WATER

A brief reference to the newer chemistry of water may fittingly be inserted at this point. It is no longer looked upon as being an inert substance consisting entirely of single molecules of H_2O , but is now thought by Armstrong³ and others to be a mixture of such simple molecules and polymers of H_2O groups. According to this view, the higher the temperature the less becomes the degree of polymerization. So that, steam alone is looked upon as being H_2O while ice is considered to consist of $(H_2O)_2$ and $(H_2O)_4$ and liquid water to be a mixture of H_2O , $(H_2O)_2$ and $(H_2O)_4$, the relative proportions of each form depending upon the temperature. The smaller open molecules are said to be chemically active, while the larger aggregates with closed groupings are inactive, as indicated in Fig. 1. The recent x ray diffraction studies of water made by Stewart⁴ may require some modifications of this conception of water and the still more recent synthesis of two

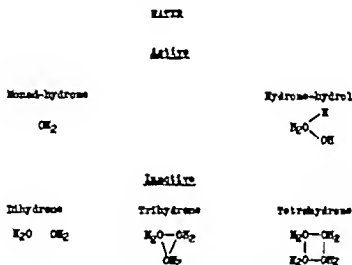


Fig. 1.—Assumed molecular constitution of water

forms of water, heavy and light, by combination of the heavy isotopes of oxygen with the heavy isotopes of hydrogen and the light with the light, promises still further modifications. Nevertheless the peculiar physical properties of water can be explained only on the basis of its being a mixture of molecules of different sizes and degrees of activity with spacial arrangements very different from those originally attributed to it.

THE PHYSIOLOGICALLY SUITABLE PROPERTIES OF WATER

This brief description of the chemical constitution of water, and an even more superficial consideration of its physical properties, will suffice to indicate why it is capable of entering into practically all of the regulatory processes of the living body and why nothing can take its place.⁵ Its unique thermal properties for instance, make possible the precise regulation of body temperature, its high surface tension serves all processes involving the phenomenon of adsorption, such as

the activity of enzymes, its high dielectric constant makes it a comparatively good insulator, while its matchless capacity as a solvent and ionization medium makes it an ideal vehicle for the transport of all essential materials to and waste products from the fixed cells of the body, as well as a medium for the innumerable chemical reactions which constitute life itself. That water plays more than a passive rôle in the body, however, is indicated by many facts and, as Mathews⁶ points out, "the younger, the more vigorous, the more alive, the more actively growing, the more impressionable cells are, the more watery they are."

CONTENT AND DISTRIBUTION IN THE BODY

The percentage water content of the body varies inversely with age in man, as well as in other species. The human embryo is 97.5 per cent

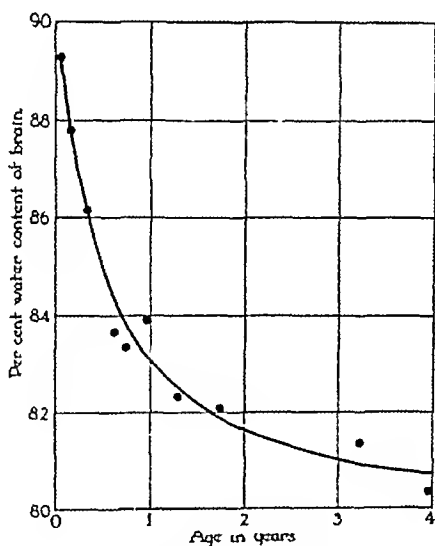


Fig. 2—Relation of water content to age in a representative organ, the brain (McQuarrie and Adolph)

water at the sixth week of life. At the end of intrauterine life (birth) the percentage of water has decreased to between 71 and 72. Varying somewhat with the amount of fat present, the body of the adult contains between 58 and 65 per cent water. The true relationship of water content to age is best illustrated in a representative organ, like the brain, which shows a diminution in percentage of water with increasing age (Fig. 2). This difference in content undoubtedly explains in part the greater water requirement of infants and their greater susceptibility to the deleterious effects of dehydration. The percentage distribution of the water in the normal human body among the various organs has been shown by Volkmann⁷ to be approximately that shown in Table I. In considering the water content from the

TABLE I

DISTRIBUTION OF WATER AMONG THE VARIOUS ORGANS (VOLKMANN)

Muscles	50.8 per cent	Brain	2.7 per cent
Skeleton	12.5 per cent	Lungs	2.4 per cent
Skin	6.6 per cent	Int.	2.3 per cent
Blood	4.7 per cent	Kidneys	0.6 per cent
Intestines	3.2 per cent	Spleen	0.4 per cent
Liver	2.8 per cent	Rest of body	11.0 per cent

practical point of view, however, it is more convenient to think of it as occurring in several compartments as defined by Gamble.⁸ These are distinguished, not only by their situation within or outside the body cells or within closed vessels, but by their composition as well. The chief distinction between the intracellular fluid or cell sap which constitutes the major portion of the body's water, and the extracellular fluids (lymph and blood plasma) is the greater concentration of colloids and of potassium and phosphorus compounds in the former and the greater mobility and greater content of sodium and chlorine in the latter. The extracellular or interstitial fluid, which occurs between the fixed cells, on the one hand, and the blood vascular bed on the other, differs in composition from the blood plasma chiefly in its lower content of colloids. Under conditions producing either dehydration or oversupply of water, it serves as an adjustable reservoir, which fluctuates in volume according to need. It serves thereby as a buffer depot, particularly for the plasma resembling in this way, to use a simile of Cannon, a swamp, which may be drained during periods of drought but which becomes inundated during times of flood. When large quantities of isotonic NaCl solution were administered to dogs by Engels,⁹ two thirds of that retained was found to be stored in the muscle depots and one sixth in the skin and subcutaneous tissues, showing these to be by far the most important reservoirs for storage of extra water. In all probability the bulk of the salt solution temporarily stored in the muscles under these conditions is taken up, not by the muscle cells themselves but by the meshwork of connective tissue surrounding them.

Intracellular water is sometimes referred to as "living water" because it is incorporated in the cell as an essential constituent of the living protoplasm. Death follows its removal just as certainly as it would the removal of the protein or lipid fractions. In considering the significance of water as a constituent of the living organism Gortner¹⁰ illustrates this point as follows. In most organisms a very considerable part of the growth process is nothing more or less than an imbibition of the bio-colloids. For example, a frog's egg, weighing on the dry basis only a few milligrams, can after fertilization be placed in a dish of filtered sterile water and allowed to undergo the process of development. Such an egg will undergo cell division, giv-

ing rise at the end of several weeks to a living tadpole which may be as much as two centimeters in length and weighing several grams. Such a tadpole has never partaken of food other than utilizing the nutrients already present in the original egg and will be found on analysis to contain less dry matter than the original egg, due to the fact that a certain amount of the organic materials present have been utilized as a source of energy and eliminated as carbon dioxide and water. The growth during these several weeks has all been due to the intake of water which has become "living water," so the tadpole is actually more than 99 per cent water. It would be ridiculous to speak of this organism as being composed of only 1 per cent of vital materials. The water is as much a part of the tadpole as are the fats, proteins, et cetera, which serve to form the gel structure, and the biochemical and biophysical reactions which take place within the cells and tissues of the tadpole are determined probably more by the water which is present than by any or all of the other constituents."

Apparently the greater portion of the water of the body occurs in the free state, that is, in a mobile form which allows it to function as a solvent, as an interactant in chemical processes and as an agent for maintaining body temperature. Its location with reference to the body cells is evidently determined chiefly by the forces of osmosis and diffusion. The remainder occurs either in loose chemical combination with various other constituents or is held fast to the cellular or the circulating colloids by the physical force of imbibition. The equilibrium between these forms, free \rightleftharpoons bound, is probably involved in certain vital phenomena. For example, Balcar, Woodyatt and Sansum¹¹ have proposed a theory of fever based upon the assumption that a strong shift in the equilibrium toward the "bound" form, when tissue colloids are injured by toxins or other agents, produce a shortage in the supply of free water necessary for dissipation of heat, thus favoring a rise in the body temperature. Much work obviously remains to be done on this interesting phase of the subject before its real significance can be evaluated.¹²

ESSENTIAL ITEMS IN WATER BALANCE

When it is desired to evaluate the total water balance of the body for diagnosis or therapeutic purposes, a complete description can be obtained only by including the items shown in Table II. A fairly complete graphic representation of the total water exchange in a twelve-year-old girl subjected to various procedures influencing the state of hydration of the body is exemplified in Fig 3, which is largely self-explanatory.

It is apparent from any set of data, showing the average values for these individual items, that the gains or losses of metabolic water may be very significant. Particularly is this so in the water balance of

young, rapidly growing subjects. A more detailed description of these particular fractions is shown in Table III. It is obvious from the latter data, indicating the extent of participation of water in the growth of tissue, why Kudo¹² and others¹⁴⁻¹⁵ have been able to maintain constant body weights in young animals, on otherwise adequate diets, by merely restricting their water intake. It is interesting to note that Kudo ob-

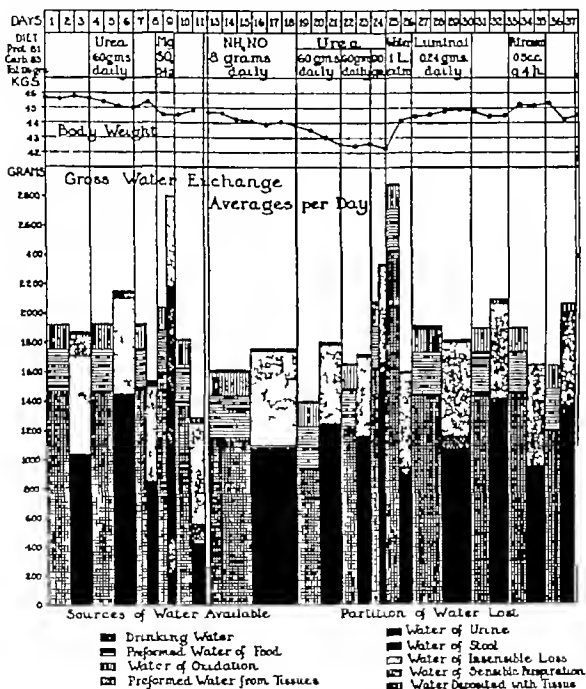


FIG. 3—Graphic representation of separate items in water balance of body under various conditions. Constant diet. Thirteen year-old girl. (McQuarrie, Manchester and Husted.)

served an ability on the part of his experimental animals to adapt themselves to a greatly restricted water intake after being on such a regimen for some time. We have often made the same observation in the case of the human subject.

The magnitude of the oxidative formation of water within the body cells is shown in Table IV. Curiously enough about 12 grams of water

is so formed on the average for each 100 calories, no matter what food is being oxidized Babcock¹⁶ has suggested that intracellularly formed water probably has greater value for the cell than water from the outside, because it tends to dilute the cell contents and so to draw nutritive substances into the cell by lowering the intracellular osmotic pressure In the light of Armstrong's theory regarding the nature of water, Cathcart¹⁷ further believes that this endogenous water may represent an active form specially suited for entrance into the metabolic activities of the body, whereas the circulating or "carrier" water may be composed largely of inactive molecules

TABLE II

INDIVIDUAL ITEMS ENTERING INTO COMPUTATION OF THE WATER EXCHANGES OF THE BODY

WATER BALANCE OF BODY	
SOURCES OF WATER	DISPOSITION OF WATER
1 Water drunk (or injected)	1 Urinary loss.
2 Preformed water of food.	2 Fecal loss
3 From oxidations in tissues	3 Insensible loss from skin and lungs
4 From syntheses and polymerizations in tissues	4 Lost in sweat secretion
5 Released from destruction of body tissues	5 Deposited with new tissues

TABLE III

RELEASE AND CONSUMPTION OF WATER IN THE COURSE OF CELLULAR ACTIVITY

METABOLIC WATER	
AVAILABLE SOURCES	HOW UTILIZED
1 From oxidations in tissues e g $C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O$	1 Combined in hydrolyses. e g $R-NH-COR + H_2O = R-NH_2 + R-COOH$
2 From syntheses in tissues e g $R-NH_2 + R-COOH = R-NH-COR + H_2O$	2 Deposited with new tissue e g 3 grams H_2O per 1 gram protein deposited
3 Preformed water from destroyed tissues e g 3 grams H_2O per 1 gram protein catabolized.	e g 0.2 grams H_2O per 1 gram fat

The quantitative importance of the preformed metabolic water as a source during fasting or marked undernutrition is indicated by the fact that approximately two-thirds of the loss in body weight consists of water The average amounts of preformed water occurring in some of the common foods are presented in Table V Water drunk as such or that administered in isotonic solutions merely supplements these primary sources The approximate amount of extra water needed for the complete metabolism of the food in an ordinary diet is indicated in Table VI

Examples of the partition of water losses from the body in normal and atrophic infants are given in Table VII. It will be seen that under ordinary conditions approximately two thirds of the output is by way of the kidneys and one third by other pathways. Water lost in

TABLE IV
WATER FORMED IN THE OXIDATIVE METABOLISM OF VARIOUS FOODS

	WATER FORMED PER 100 GRAMS	WATER FORMED PER 100 CALORIES
	c.c.	c.c.
Pure fat	107.1	11.5
Pure carbohydrate	56.0	13.8
Pure protein	41.3	10.3
Bread	33.0	12.9
Potatoes	11.2	12.2
Milk, cow's	8.0	12.2
Milk, human	8.7	12.3
Egg yolk	42.3	11.3
Egg white	7.5	11.4
Chicken lean cooked	15.3	11.2
Beef, medium fat, cooked	24.0	11.0

sensibly by way of the skin and lungs is a factor of the utmost practical significance, not only because of its relative magnitude as an item in the water balance but also because under standard environmental conditions (temperature range between 20° and 24° C. and relative

TABLE V
WATER CONTENT OF SOME COMMON FOODS USED BY INFANTS AND CHILDREN

FOOD MATERIAL	WATER CONTENT PER CENT BY WEIGHT	WATER CONTENT GM. PER 100 CAL.
Colostrum	85	119
Human milk	87	130
Cow's milk	87	130
Whole lactic acid milk plus 7 per cent sugar	82	97
Unsweetened evaporated milk	73	1
40 per cent cream	78	15
Butter	15	1
Cream cheese	34	82
Egg yolk	49	13
Egg white	86	156
Veal leg	60	44
Beef sirloin	54	25
Fresh ham	48	17
Fish halibut	75	60
Bread average white	30	14
Zwieback	5	1
Bananas	75	74
Potatoes	63	96
Spinach	83	220
Tomatoes	94	430
Carrots or beets	87	187
Orange	86	163
Apple	63	132

humidity between 30 and 60 per cent) and under circumstances not requiring strenuous muscular activity, approximately one-fourth of the heat produced in the body is dissipated in the process of its vaporization, as first shown by Soderstrom and DuBois¹⁸ On the basis of the latter fact, a fairly accurate gravimetric method for predicting the total heat production of the body has been developed by Benedict and Root¹⁹ and further elaborated by Johnston and Newburg²⁰ and by Levine and his coworkers²¹ Correspondence between the average insensible loss (insensible loss = insensible water + CO₂ exhaled - O₂

TABLE VI

GRAMS OF WATER NEEDED FOR COMPLETE METABOLISM OF 100 CALORIES OF SOME FOOD SUBSTANCES

	PREFORMED WATER	GAINED BY OXIDATION	LOST IN DISSIPATING HEAT	LOST IN EXCRETING END PRODUCTS	DEFICIT
Protein	0	10.3	60	300	350
Starch	0	13.9	60	0	46
Fat	0	11.6	60	0	48
Beef, sirloin	25	11.3	60	119	143
Fish, cod	120	10.4	60	382	312
Eggs, hen	47	11.1	60	154	156
Milk, whole	127	12.5	60	123	43
Bread	14	13.2	60	69	102
Apples	150	13.9	60	56	-48

TABLE VII

PARTITION OF WATER OUTPUT IN INFANTS UNDER HOSPITAL CONDITIONS IN PER CENT OF TOTAL

URINE PER CENT	SKIN AND LUNGS PER CENT	FECES PER CENT	REFERENCE
60.0	33.5	6.5	Breast fed (Rubner)
63.9	20.5	15.6	Atrophic (Rubner)
71.7	25.9	2.4	Bottle-fed (Niemann)
75.2	22.6	2.2	Atrophic (Bahrdt)

simultaneously inhaled) per hour and the total heat production per 24-hour period is sufficiently close to make possible reliable predictions from standard tables. An increase of one gram of insensible loss per hour is equivalent to approximately 32 calories in the 24 hours (Table VIII). In our own work we have found that the state of hydration of the body may influence the insensible water loss without significantly altering the total heat production, dehydration diminishing and superhydration increasing the output²² (See Table IX, Fig 4.)

The percentage of the total body heat, which is dissipated by vaporization of water, rises rapidly with increasing environmental temperature. This rises from 17 per cent at 15° C to 100 per cent when the environmental temperature equals or goes above that of the body.

Barbour²³ has shown that the first response of the body to a rise in the environmental temperature above the critical level for sweating (30°C) is dilution of the blood by water mobilized from the tissues. While it is unlikely that this mechanism is in any way at fault in congenital ichthyosis, the absence of sweat glands in severe cases of this disorder greatly limits the ability of such persons to indulge in vigorous exercise or to withstand high temperatures. They tend to develop fever whenever the need for dissipating extra heat appears. Their insensible perspiration is, nevertheless, entirely normal.

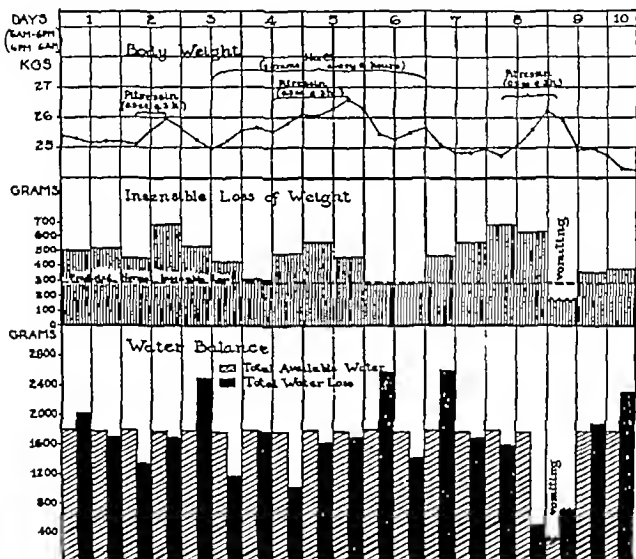


Fig. 4.—Effect of superhydration, as produced by forced water drinking and pituitary antidiuretics, on insensible perspiration. Diet low in protein and minerals. Effect of added NaCl. Boy aged nine years wt. 6 kg. (Manchester Hospital and McQuarrie.)

WATER REQUIREMENTS OF THE BODY

The requirements of the body for water can now be estimated fairly closely if all significant conditions are known. They vary with such factors as age, muscular activity, temperature and humidity of the surroundings, type of diet and of course with the functional state of the various organ systems. The requirement in terms of age and size roughly parallels the total energy metabolism. It is, therefore, several times greater per unit of body weight during infancy than during

TABLE VIII

TWENTY FOUR HOUR HEAT PRODUCTION PREDICTED FROM THE HOURLY INSENSIBLE LOSS OF WEIGHT (MODIFIED FROM BENEDICT AND ROOT)

INSENSIBLE LOSS GRAMS	PREDICTED HEAT CALORIES	INSENSIBLE LOSS GRAMS	PREDICTED HEAT CALORIES
14 0	900	36 5	1606
14 5	916	37 0	1622
15 0	932	37 5	1638
15 5	948	38 0	1655
16 0	965	38 5	1670
16 5	981	39 0	1685
17 0	997	39 5	1700
17 5	1012	40 0	1715
18 0	1028	40 5	1730
18 5	1043	41 0	1745
19 0	1059	41 5	1760
19 5	1074	42 0	1775
20 0	1090	42 5	1791
20 5	1106	43 0	1807
21 0	1122	43 5	1823
21 5	1138	44 0	1840
22 0	1155	44 5	1855
22 5	1170	45 0	1870
23 0	1185	45 5	1885
23 5	1200	46 0	1900
24 0	1215	46 5	1916
24 5	1231	47 0	1932
25 0	1247	47 5	1948
25 5	1263	48 0	1965
26 0	1280	48 5	1980
26 5	1296	49 0	1995
27 0	1312	49 5	2010
27 5	1328	50 0	2025
28 0	1345	50 5	2040
28 5	1360	51 0	2055
29 0	1375	51 5	2070
29 5	1390	52 0	2085
30 0	1405	52 5	2100
30 5	1421	53 0	2115
31 0	1437	53 5	2130
31 5	1453	54 0	2145
32 0	1470	54 5	2161
32 5	1485	55 0	2177
33 0	1500	55 5	2193
33 5	1515	56 0	2210
34 0	1530	56 5	2226
34 5	1545	57 0	2242
35 0	1560	57 5	2258
35 5	1575	58 0	2275
36 0	1590	58 5	2291

adult life The average amounts of water required by children of different ages under ordinary conditions are shown in Table X

In vigorous muscular exercise the water requirement is raised by about three-fourths of one gram for each large calorie of extra heat so produced With high environmental temperatures, such as occur in summer or even in winter in overheated nurseries, loss of water by way of the skin may double or even quadruple the ordinary requirements From a combination of the two factors, strenuous muscular

TABLE IX

(COMPARISON OF VALUES FOR HEAT PRODUCTION AS DETERMINED GASOMETRICALLY AND BY THE INSENSIBLE LOSS METHOD UNDER NORMAL CONDITIONS AND IN DEHYDRATION. INSENSIBLE PERSPIRATION AS ACTUALLY MEASURED AND AS PREDICTED FROM GASOMETRIC METABOLISM MEASUREMENTS COMPARED. J. R., AGED SIXTEEN YEARS, WEIGHT 48 Kg (FROM MANCHESTER, HURST AND MCQUARRIE.)

DIET (1712 CAL.)	MEAN ROOM TEMP C.	MEAN RELATIVE HUMIDITY PER CENT	BODY WEIGHT KG	NET CHANGE IN BODY WATER (GM.)	DEGREE OF DEHYDRATION	TOTAL CALORIES FOR PERIOD (12 HOURS)			INSENSIBLE PERSPIRATION FOR PERIOD (12 HOURS)		
						DET D (TISSOT)	PREDICTED FROM INS. LOSS	PER CENTAGE DIFFERENCE	MEASURED	PREDICTED FROM TISSOT	PER CENTAGE DIFFERENCE
Borderline Venketogenic	24.0	70	47.41	0	None	6.9	657	- 0.3	32.8	327	- 0.3
	22.0	73	40.55	-914	Moderate	030	580	- 9.2	206	312	-14.7
	23.0	66	47.60	+950	None	030	650	+ 3.2	319	310	+ 2.9
Ketogenic	22.5	64	46.62	0	Slight	672	6.4	- 3.2	323	340	-5.3
	21.3	58	45.30	-1308	Fully Marked	666	560	-10.0	251	331	-24.1
High Protein	23.6	68	46.40	0	Moderate	093	014	-11.4	293	350	-16.3
	22.0	72	40.76	+300	Slight	694	630	- 9.0	303	350	-13.4
	22.5	61	45.42	-1233	Fairly Marked	004	500	-24.7	205	330	-38.0
	22.2	51	44.53	-2087	Fairly Marked	652	518	-21.0	220	324	-32.0
	23.0	50	43.00	- 172	Fairly Marked	639	508	-21.8	212	312	-32.0

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20 0	1090	42 5	1791
20 5	1106	43 0	1807
21 0	1122	43 5	1823
21 5	1138	44 0	1840
22 0	1155	44 5	1855
22 5	1170	45 0	1870
23 0	1185	45 5	1885
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24 0	1215	46 5	1916
24 5	1231	47 0	1932
25 0	1247	47 5	1948
25 5	1263	48 0	1965
26 0	1280	48 5	1980
26 5	1296	49 0	1995
27 0	1312	49 5	2010
27 5	1328	50 0	2025
28 0	1345	50 5	2040
28 5	1360	51 0	2055
29 0	1375	51 5	2070
29 5	1390	52 0	2085
30 0	1405	52 5	2100
30 5	1421	53 0	2115
31 0	1437	53 5	2130
31 5	1453	54 0	2145
32 0	1470	54 5	2161
32 5	1485	55 0	2177
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total daily water exchange of between seven and eight kilograms and gives the history of having passed as much as four gallons or about 16 kilograms of urine in one day although his present body weight is only 11 kilograms. The mechanism of this disorder is discussed at greater length below.

Adolph²² has summarized the coefficients for calculating the water requirements of an essentially normal individual in cc per 24 hours, from the surface area of the body (in sq m) and the total caloric

TABLE X

RANGE OF AVERAGE WATER REQUIREMENT OF CHILDREN AT DIFFERENT AGES UNDER ORDINARY CONDITIONS

AGE	AVERAGE BODY WEIGHT IN KILOGRAMS	TOTAL WATER IN 24 HOURS	WATER PER KILO BODY WEIGHT IN 24 HOURS
3 days	3.0	240-300	80-100
10 days	3.2	400-480	125-150
3 months	5.4	750-804	140-160
6 months	7.3	950-1120	130-155
9 months	8.6	1075-1,240	125-145
1 year	9.7	1,140-1,300	120-135
2 years	11.8	1,350-1,475	115-125
4 years	16.2	1,600-1,800	100-110
6 years	20.0	1,800-2,000	90-100
10 years	28.7	2,000-2,440	70-85
14 years	45.0	2,250-2,700	50-60
18 years	54.0	2,160-2,700	40-50

TABLE XI

AVERAGE RATES OF SECRETION OF DIGESTIVE FLUIDS IN ADULT MAN (ROWNTREE)

SECRETIONS	AMOUNT C.C.	AUTHORITY
Saliva	1500	Blüder and Schmidt
Gastric juice	2000 to 3000	Blüder and Schmidt
Bile	500 to 500	Pfaff and Balch
Pancreatic juice	500 to 800	Wohlgenuth
Succus entericus	8000	Pregl
Approximate Total	8000	

requirements (in large cal) as shown in Table XII. While this is obviously not a precise practical method it serves to emphasize the approximate magnitudes and the range of variations in the requirements.

REGULATION OF WATER CONTENT AND EXCHANGES

Fortunately the body has more or less automatic mechanisms for maintaining an optimum content of tissue water. Thirst, which is apparently a sensation dependent upon some degree of deficit in the free water of the salivary glands and mucous membranes of the mouth²³ is usually a trustworthy indicator of the body's need for water. Little concern need be felt regarding the possibility of a person's taking too much water excepting in a very limited number of

pathological states which will be referred to later. Extra water taken, if unaccompanied by sodium chloride in or near isotonic concentration, is fairly promptly excreted by the kidneys with but little effect upon the general body metabolism. While the mechanism of this water diuresis is not perfectly understood, Marx³⁰ claims that the blood is diluted shortly after water is drunk, and to almost the same extent whether the amount taken is 1000, 500 or as little as 50 c c. Because of the latter fact he assumes that the intake of water starts a complicated chain of reactions between the blood and the tissues, involving the whole mechanism of water metabolism and finally resulting in diuresis of the excess water. That dilution of the blood results in the calling into activity of an increased number of renal glomeruli is indicated by the work of Richards.³¹ The influence of a nervous or

TABLE XII

COEFFICIENTS FOR CALCULATING THE WATER REQUIREMENT OF AN INDIVIDUAL, IN C C PER 24 HOURS, FROM THE SURFACE AREA OF THE BODY (A) AND THE CALORIC REQUIREMENT (E)

Growth	0	15 A	30 A
Basal urinary	400 A	1,000 A	1,500 A
Basal fecal	30 A	90 A	150 A
Basal extrarenal	250 A	390 A or	
Exercise (sweat)	$173 \times 0.4 E$	$173 \times 0.25 E$ basal	
Temperature (sweat)		$173 \times 0.55 E$ exercise	
Total	2,100	1,800 A (C -32)	
(approximate)		3,400	5,000

psychic factor has also been demonstrated by Bykow and Belkman³² and by Marx,³³ who found that blood dilution occurred in trained dogs through the mechanism of conditioned reflexes without the administration of extra water and in a hypnotized man following mere suggestion of water drinking.³⁴ When isotonic NaCl solution is taken instead of water, there is but slight diuresis and blood dilution persists longer. Comparatively enormous amounts of water may be stored in the extracellular reservoirs of the body without harm, if it is given in the form of Ringer's solution.

Administration of excessive amounts of tap water (50 c c per kg per hour) to normal animals was found by Rowntree and his coworkers³⁵ to produce a symptom complex which they designate as "water intoxication." This syndrome consists of restlessness, muscle tremors, vomiting, diarrhea, incoordination, prostration, generalized convulsions and finally death, if water administration is continued. These signs are much less severe or do not develop at all, however, if physiological saline solution is given instead of tap water. Snell and Rowntree³⁶ described the case of a man with severe diabetes insipidus with compulsive thirst, who developed these symptoms spontaneously on

several occasions when he drank enormous quantities of tap water (20 quarts in twenty four hours) In collaboration with Thompson and Johnson, the author has recently had the opportunity to study the water and mineral balances in a child with diabetes insipidus who repeatedly had convulsions when a small excess of water was stored following pitressin administration Miller and Williams³⁷ produced as thenia muscle cramps, headache dizziness and elevated blood pressure, but no convulsions, in a human subject when they administered 10 quarts of water directly into the duodenum by Rehfuess tube The body weight of this subject was increased from 124 to 142 pounds in a period of twelve hours Harding and Harris³⁸ found 10 per cent NaCl to be the most efficient antidote for 'water intoxication' Rowntree³⁹ attributes the symptoms to a disturbance of the normal balance between the various electrolytes of body fluids Smyth and coworkers⁴⁰ from a more recent study of the mechanism involved, conclude that the essential cause of the convulsions is alkalosis due to loss of gastric Cl

According to the investigations of Lauson and Roca⁴¹ and of Pick⁴² and his coworkers the sequence of events resulting from the liberal administration of fluid in the normal subject is as follows The liver acts as a temporary reservoir for a considerable portion of the excess water taken thus preventing sudden overloading of the right side of the heart The liver then diminishes in size gradually as the stored fluid escapes into the general circulation by way of the lymphatics In the normal dog diuresis from water ingestion was found by Molitor and Pick⁴³ to begin not earlier than 50 to 60 minutes after water was given and lasted for three or four hours, while in the dog with an Eck fistula (which largely excludes the liver from the circulation) extra water began to appear in the urine within 20 to 30 minutes and the diuresis required but half the normal time for its completion

The mechanism by which the liver performs this function as a temporary reservoir is apparently as follows Through the reflex activity of the sympathetic vasomotor system (as confirmed by adrenalin injections) constriction of the hepatic veins and closing of their valves follows the ingestion of the fluid, thus causing partial obstruction to the outflow from the liver Simultaneously with this the pressure in both the hepatic artery and the portal veins increases causing thereby increased filtration pressure in the liver capillaries with gradual outflow of water into the lymph spaces and finally into the thoracic duct Excess water taken as such is then fairly promptly excreted by the kidneys whereas isotonic NaCl solution is secondarily stored for a longer time in the extracellular depots of the body particularly in the muscles and skin as previously pointed out In liver disease this temporary storage function is said to be impaired as indicated by greater dilution of the blood following water administration⁴⁴

INTERCHANGE OF WATER THROUGH LIVING MEMBRANES

Revolving around the problem of edema, much study has been devoted in recent years to the mechanism of interchange of fluid between the blood capillaries, on the one hand, and the lymph or tissue spaces (intercellular reservoir), on the other. Since the subject has been adequately summarized in recent papers by Leiter,⁴³ Landis⁴⁴ and others, however, little need be said of it here excepting to enumerate the chief factors concerned. Starling's⁴⁵ original claim, that the outflow of fluid from the capillaries is dependent upon the hydrostatic pressure of the blood within them and that the inflow from the tissues is dependent upon the colloidal osmotic pressure of the plasma, has been adequately substantiated, i.e., when the hydrostatic pressure at the venous end of the capillaries is greater than the osmotic pressure of the plasma proteins, edema will occur. Colloidal osmotic pressures below 19 to 20 mm of mercury,⁴⁶ corresponding with a total plasma protein range below 5.5 ± 0.3 per cent or a plasma albumin range below 2.5 ± 0.3 per cent or plasma specific gravity below 1.022,⁴⁷ favor the occurrence of edema. As pointed out by Landis and others, there are undoubtedly additional factors of importance, particularly under abnormal conditions. Chief among these factors are tissue pressure, amount of protein which has escaped into the fluid outside of the capillaries, local temperature and state of oxygenation of the blood. Injury of any kind to the capillary walls results in increased permeability not only to water and simple crystalloids but to plasma proteins and lipids as well. Many of these factors are undoubtedly involved also in the passage of fluids through the epithelial as well as the endothelial cells in the special organs, such as the kidneys, the cerebrospinal system, the gastrointestinal tract and various purely secretory structures, but much still remains to be learned regarding the exact mechanisms of transfer in these complicated systems.

The factors regulating exchange of water between the intracellular and the extracellular compartments have not been studied extensively, although they are undoubtedly of the utmost importance to the organism. In addition to certain of those enumerated above, there are unquestionably others to be considered, such as the different mineral patterns of the fluids on the two sides of the cell membrane, the acid base equilibrium, the type of metabolic process predominating within the cells, the physicochemical peculiarities of the cell colloids and membranes, and lastly certain extrinsic nervous and endocrine factors. Considered in this light, it is obvious that cellular activity must be accompanied by continuous changes in the water distribution between the cells and their immediate environment.

EFFECTS OF VARIOUS IONS

While any shift in the acid base equilibrium of the body fluids toward the alkaline side appears to favor the retention of water by the tissues,⁴⁸ the Na ion, in contrast with all others, appears to be more or less specifically active in this regard. While Br behaves very similarly to Cl, attempts to replace Na by other cations, as for instance K, usually results in water loss rather than storage. A shift of the acid base balance toward the acid side results in loss of body water. The action of mineral acids and acid forming salts, such as NH_4Cl , CaCl_2 and NH_4NO_3 , is similar to that of the ketogenic type of acidosis and the acidosis of severe diarrhea, in causing a loss of body water. While increase in the H ion concentration *per se* may be important because of its direct influence on the capacity of the colloids to hold water the loss of Na which occurs under such conditions is probably the more potent factor. Fenn⁴⁹ has recently found that K migrates into or from muscle cells in company with OH and not with other anions. Potassium, therefore tends to shift from an intracellular to an extracellular position when the OH concentration within the cell is greater than that in the fluids outside of the cell. The direction is reversed when the pH of the extracellular medium is higher than that of the cell fluid. Presumably water translocation accompanies such shifts. Haldé and his coworkers⁵⁰ in a study of the factors affecting hydration of nervous tissue *in vitro* found that different parts of the brain swell to a certain degree when placed in distilled water. They then found that the anions of various K salts inhibit water absorption by the tissues in the following order: citrate > tartrate > oxalate > SO_4 > acetate > CNS > Br > NO_3 > Cl > I. In the cation series the divalent ions were found to inhibit swelling more effectively than monovalent ions. The cations of Cl inhibited the taking up of water as follows: Ca, Ba, Sr > Na Li > K Cs Rb.

INFLUENCE OF DIET

Beyond the facts first that a minimum amount of water is required for the excretion of the nonvolatile end products of catabolism (100 c.c. for every 45 grams urea and 65 c.c. for each gram of ash), second that prolonged protein deficiency causes water retention secondary to the lowering of the plasma protein content and third, that ketogenesis promotes loss of body water, as already indicated the dietary has but little influence on water regulation. The claim that carbohydrate *per se* has a specific water retaining effect has not to my knowledge, been adequately substantiated by uncomplicated experimentation. The impression, that a high carbohydrate diet results in storage of excess water in the tissues probably originated from observations made on so-called hydrolabile infants and older subjects suffering from genuine

nutritional edema It has been well established that the vast majority of such patients retain water because of the low plasma protein which results from a deficiency of protein in the diet It is probably true that the edema found in the "moist" type of beriberi is explainable on the same basis⁵¹ Of course, carbohydrate has a specific effect in checking the excessive water loss due to the ketogenic type of acidosis merely by virtue of its effect in counteracting ketogenesis

RÔLE OF PHOSPHOLIPIDS AND CHOLESTEROL

That the balance in the tissues between the physiologically antagonistic substances, cholesterol and lecithin, may be an important factor in water metabolism is indicated, not only by the fact that the former is lyophobic and the latter lyophilic, but even more directly, by the finding of Degkwitz⁵² that cholesterol administered parenterally results in active diuresis while lecithin causes water retention Dahmlos and Solé⁵³ found that lecithin and OH^- together favor an oil in water dispersion system, while cholesterol and H^+ are antagonistic to the formation of such a system They, therefore, conclude that lipids constitute a very important factor in the penetrability of membranes by water and electrolytes Cholesterol injected intravenously was found by these authors also to cause temporary hydremia and an increase in plasma Cl which resulted later in an increased output of both water and Cl in the urine Lecithin is reported to have had an opposite effect In this connection it is interesting to note that Haustein⁵⁴ found the serum cholesterol to be low in a series of hydro-labile children

ENDOCRINE AND NERVOUS FACTORS

The most important extrinsic factors in the regulation of the water metabolism are the interrelated endocrine and nervous influences Of the former, the secretion from the posterior lobe and pars intermedia of the pituitary body is unquestionably the most potent This was first discovered in 1901 by Magnus and Schafer,⁵⁵ who found it to have a diuretic action when injected into the anesthetized animal Not until 12 years later was its more important antidiuretic action in the un-narcotized subject discovered by von den Velden⁵⁶ In a heart-lung-kidney preparation made in such a way that the pituitary body could be inserted at will, Starling and Verney⁵⁷ found that the effect of its presence in the circuit was to interrupt the flow of urine They observed in a similar preparation that the antidiuretic activity following pituitary extract was accompanied by an increased chloride excretion⁵⁸ Motzfeldt⁵⁹ first proved its antidiuretic effect during polyuria due to oral administration of large quantities of water, while von den Velden demonstrated its effectiveness in stemming the flow of urine in diabetes insipidus when injected subcutaneously Blumgart⁶⁰ later found that it is just as efficient in controlling the polyuria of diabetes

insipidus when sprayed intranasally as when given by hypodermic injection. In a special study on the diphasic action of pituitrin McFarlane⁴¹ found that high speed intravenous injection, like light ether anesthesia, tends to favor a diuretic response, while slow intravenous injection inhibits urinary flow.

McQuarrie and Peeler⁴² made the observation that there is a significant net loss in body weight following a period of sustained pituitary antidiuresis when the subject is on a low mineral, high water intake. Thompson, Ziegler and McQuarrie⁴³ have found this procedure to be effective in reducing certain types of edema. In several instances the equivalent of the well known 'spontaneous diuresis' has apparently been initiated by the procedure when the level of the serum proteins at the time of the test was not far below the critical point for edema formation. This weight reducing effect is apparently dependent upon the extra excretion of salt during the period of antidiuresis.

The mechanism by which this hormone produces antidiuresis is still the subject of controversy, some workers believing that it acts directly on the renal mechanism, others that it affects the other tissues of the body primarily. The latter observers consider that the kidneys function in a purely secondary manner in response to changes in the blood circulating through them. It seems highly probable that the action is a complicated one involving both the kidneys and the general body tissues simultaneously. Richards and Plant⁴⁴ found by direct observation that the first response to the extract was constriction of the efferent glomerular vessels, which produced a temporary diuresis while a later more striking response was constriction of the afferent vessels which resulted in antidiuresis. According to Geiling⁴⁵ increased reabsorption from the kidney tubules resulting from a specific effect of infundibular extract on the tubular epithelium may be largely responsible for the antidiuresis. Marshall⁴⁶ has recently obtained convincing evidence that the loop of Henle may be the chief site of antidiuretic action in the kidney. Excretion of potassium chloride, urea and other substances given by mouth with one liter of water was found by Adolph and Ericson⁴⁷ not to be inhibited by intramuscular injections of pituitrin. These authors found that the amount of water excreted under these conditions was limited to that for removing the excess salt the remainder being retained. They concluded that the extract acts by rendering the kidneys insensitive to excess water in the blood plasma.

That pituitrin affects other tissues as well as the kidneys is indicated by the finding that salivary, gastric and intestinal secretions are inhibited by its injection^{48, 49}. At the same time lymph flow decreases and its protein content increases. Hydremia and mobilization of electrolytes from the tissues into the blood stream occur following injection of pituitary extract, even after bilateral nephrectomy⁵⁰. Stehle⁵¹

finding an increased urinary excretion of various salts during anti-diuresis, concluded that the effect of pituitrin is to mobilize electrolytes into the blood and in so doing renders the tissues capable of taking up more water. On the basis of this, he advances the theory that in diabetes insipidus the failure of the body to retain water is due to a reversal of the electrolytic conditions found in the tissues when pituitary extract is administered. Barbour and his associates⁷¹ found an increase in the water content of the cerebrum, medulla and basal ganglia and in the muscles and liver, following pitressin injection, whereas they found a decrease in the skin and subcutaneous tissues. From water vapor studies by Hill's method, it was found by Barbour that water administration tended to produce less of an osmotic pressure fall after pituitary extract than it did in the absence of this substance. Yet the blood specific gravity fall was decidedly greater. The author interprets this as an indication that the pituitary hormone causes mobilization into the blood of a slightly hypertonic salt solution. He concludes that the kidney is tending to assume a minor rôle as a primary locus of water shifting after pituitary administration.

Glass,⁷² who likewise found the water content of striated muscle markedly increased by injection of pituitary extract, considered this control of tissue swelling by pituitrin to be dependent upon nerve action because sympathectomy as well as extirpation of the centers of the midbrain markedly affected the water content of the muscles. Hypertonic solutions interfere with the hypophyseal influence on tissue swelling by preventing escape of plasma water to the tissues. According to Janssen,⁷³ section of the spinal cord at the level of the fifth cervical interspace does not interfere with the action of posterior pituitary extract. Hoff and Potzl⁷⁴ obtained contrary results. Oehme and Oehme⁷⁵ found the extract to exert its antidiuretic effect after complete degeneration of the renal nerves. In clinical hyperpituitary disease Marx⁷⁶ finds that water ingestion causes a long-lasting hydremia, while in hypopituitary disorders anhydremia may result from a simple Volhard water-drinking test.

It has been established by the recent work of Pines⁷⁷ and Greving⁷⁸ that the pars intermedia and the posterior lobe of the pituitary gland are under central nervous control through fibers originating in the nucleus supraopticus and possibly nucleus paraventricularis. Apparently it is injury to this tract of fibers or then central nuclei which causes the marked polyuria, demonstrated by Camus and Roussy,⁷⁹ Ashner⁸⁰ and Bailey and Bremer⁸¹ to follow puncture in that region. Houssay and Hug⁸² found the polyuria in this experimental form of diabetes insipidus to be primary and not dependent upon polydipsia, glycosuria or increase in blood pressure. Denervation of both kidneys prior to puncture in the region of the hypothalamus, according to them, does not prevent the polyuria. The latter is controlled, however,

by subcutaneous or intranasal administration of posterior pituitary extract. Clinical diabetes insipidus due to tumor growth or to an inflammatory lesion involving the region of the tuber cinereum or hypothalamus, resembles this experimental form in every way.

Cushing and Goetsch²² were the first to identify posterior pituitary secretion in the cysternal and ventricular fluids. They did not find it, however, in the spinal subarachnoid spaces. Höff and Wermer²⁴ found that either strong emotional stimuli or administration of diuretics leads to an increase in the amount present in the cerebrospinal fluid. Karplus and Peczenik²⁵ demonstrated a similar response to electrical stimulation of the tuber cinereum. Höff and Wermer interpret the response to administration of diuretics as a compensatory reaction on the part of the body to prevent excessive loss of water. Cushing²⁶ has more recently discovered that direct introduction of pitressin into the third ventricle in man causes a typical parasympathetic, or pilocarpin-like, response with flushing of the skin and visible sweating, while in intramuscular or subcutaneous injection, of course produces a typical sympathetic reaction. The spinal anesthetic avertin, and atropine both prevent the parasympathetic response from intraventricular administration. This newer work on the action of the pituitary secretion and the vegetative centers in the diencephalon serves to emphasize still further the fact that the neuroendocrine mechanism plays a predominating rôle in the regulation of the water metabolism.

The extreme polyuria of experimental or clinical diabetes insipidus has long suggested the elaboration in the body of diuretic hormones which are normally balanced by the antidiuretic pituitary secretion. Bourquin²⁷ and Ohvet²⁸ have both reported the presence of a strongly diuretic extract from the diencephalon. Bourquin obtained such a diuretic principle from the region of the mammillary bodies, but not elsewhere in the brain in dogs with experimental diabetes insipidus. She found the same substance in the blood and urine of these dogs but not in normal animals. Trendelenburg²⁹ using slightly different technique, failed to confirm these findings. Teel³⁰ reported finding a markedly diuretic substance in an extract from the anterior lobe of the pituitary body. To my knowledge this has not as yet been confirmed by other workers. The observation of Hann³¹ however is of special interest in this connection. He demonstrated that polyuria ceased terminally in cases of diabetes insipidus due to lesions of the posterior lobe of the hypophysis when the lesion gradually encroached upon and destroyed the anterior lobe.

Pick³², Glaubach and Molitor³³, Porges³⁴ and Grossman³⁵ have all reported the presence of a strongly diuretic principle in the liver, administration of which is said by Pick to be effective in certain cases of nephrosis and in nremia from experimental reduction of kidney substance. Ivy³⁶ has demonstrated that secretin has a mildly diuretic

effect Although there is no definite proof of such a relationship, it is barely possible that these substances play a special rôle in water diuresis

Eppinger⁹⁷ demonstrated the importance of the thyroid hormone in water metabolism, showing it to have a mildly diuretic action E Z Epstein⁹⁸ and others have shown that this diuretic effect of thyroxin is due, not to any direct action on the kidneys, but to its mobilizing fluid from the tissues into the blood Pituitrin inhibits the diuresis of thyroxin In myxedema or cretinism, thyroid extract causes removal of stored water and NaCl from the tissues in a specific manner Ordinary diuretics acting primarily on the kidneys do not remove the excess fluid in such cases In some types of edema parathyroid extract has been shown by Mason,⁹⁹ Meakins,¹⁰⁰ McCann,¹⁰¹ Reitzel and Stone,¹⁰² and others to exert a diuretic action We have also seen striking examples of this effect The observation by Baar¹⁰³ of increased water in the brain tissues of subjects with infantile tetany is interesting in this connection This author considers the increased hydration of the brain tissue to be of primary significance in the symptom complex Parathormone, of course, is specific in relieving this type of overhydration Ellis¹⁰⁴ has reported a similar increase in water content of the brain in guanadine tetany, as well as in the tetany of experimental parathyroprevia

Drabkin¹⁰⁵ and others have demonstrated the tissue hydrating effect of insulin and have pointed out the importance of water in the action of insulin on the carbohydrate metabolism According to Drabkin, insulin convulsions appear to be more closely related to increased hydration of the brain tissue than to the hypoglycemia *per se* The retention of fluid which follows administration of insulin in cases of severe diabetes mellitus with dehydration often goes beyond the point of normal rehydration to one of edema formation¹⁰⁶ Schiff and Choremis¹⁰⁷ showed that dehydration decreases the efficiency of carbohydrate metabolism and insulin action Whether or not an endocrine factor is involved in the water retention associated with obesity is not known The circulatory factor is probably sufficient to account for the phenomenon in most instances

That the internal secretion of the adrenal cortex plays an important rôle in the regulation of the fluid balances of the body is indicated by the recent reports of Swingle¹⁰⁸ and coworkers and by Silvette¹⁰⁹ The former found that water enters the tissues from the vascular system at an abnormally rapid rate in adrenalectomized animals, causing the blood volume to shrink and the blood pressure to fall progressively to the death level, unless an extract of the gland is administered Silvette found that adrenalectomized rats excrete less urine and more chlorides than normal animals under the same fasting conditions A definitely reduced ability to eliminate injected fluids was found in

animals suffering from cortical insufficiency. The muscles and parenchymatous organs of animals with adrenal insufficiency showed a higher water content than normal, while the blood showed concentration, from which the author concludes that the impaired ability of the kidneys to excrete water is extrarenal in origin.

STATE OF HYDRATION AND RESISTANCE TO INFECTION

The relationship of states of hydration to infections, quite apart from that involved in heat loss by vaporization of water during fever is very important. Barhour¹¹⁰ and Underhill¹¹¹ have shown that the blood tends to become concentrated early in the course of a febrile illness. In fever dilution of the plasma precedes a fall in temperature from the use of antipyretics according to the work of Barhour. Apparently a similar mobilization of water from the tissues into the blood frequently accompanies the natural termination of fever in the acute infectious diseases. Sandelowsky¹¹² was the first to study the blood concentration, salt balance and weight changes in patients with pneumonia. In seven of his eleven cases the body weight either increased or remained stationary during the febrile period but fell rapidly after the crisis. The four remaining cases showed a precritical loss of weight. In a study of the total base and chloride metabolism in relation to salt and water retention in infants with primary pneumonia, Wilder and Drake¹¹³ observed a negative base and chloride balance, when the intake of these ions was low, but a markedly positive balance when the intake was high before the crisis. In the former case the base and chloride of the plasma were low and the weight loss was rapid whereas in the latter, those values were normal or elevated and the weight was increased often with visible edema. Rapid excretion of the stored water and salt accounted for the post critical loss in body weight. A direct relationship between the mortality rate and the degree of water retention was suggested by the data. These authors, therefore advise the use of a known NaCl intake (15 cc 0.1 N NaCl solution per pound of body weight in 24 hours) to prevent water retention. Sunderman and Anstin¹¹⁴ confirmed these findings as regards water retention in pneumonia and showed definitely that there was a percentile increase in the water content of the tissues during several precritical days. While the evidence for water shifting due to infection is more spectacular in pneumonia than in most febrile illnesses the same general reaction appears to be common to all diseases of this class and to serum sickness as well.¹¹⁵ That water shifting is involved in the related allergic phenomena is indicated by the experimental studies of Rubin and Kellett¹¹⁶ who found that dehydration has a strongly protective reaction against the harmful effects of anaphylactic or histamine shock. Chronic water logging of the tissues apparently lowers the resistance to acute infection, as attested by the well

known increase in susceptibility of so-called hydrolabile infants and of patients with nephrosis and chronic cardiac anasarca Preliminary experiments now being conducted in our clinic by Doctor Ross Weisiger suggest, so far as they go, that the optimum state of hydration for resistance to acute infection may be one of mild dehydration

WATER CONTENT AND FUNCTIONAL ACTIVITY OF NERVOUS TISSUE

The possible relationship between the state of hydration of nervous tissue and increased irritability has already been alluded to in our discussion of "water intoxication," tetany and the mechanism of insulin convulsions From what little evidence is available, it appears to be a rule that the greater the degree of hydration, the more irritable nervous tissue is Of course, the fact that the various electrolyte equilibria and other factors are often equally important must not be overlooked It seems probable that the increased ease with which infants and young children have convulsions, as compared with adults, may depend in part upon the significantly greater water content in their brains Whenever nerve tissue is injured, it imbibes water and becomes more irritable

Barbour and his coworkers¹¹⁷ have demonstrated an increase in the water content of the brain produced by withdrawal of morphine from morphine addicted dogs This increased hydration of the brain tissue is given by them as the cause of the nervous tremors and increased excitability in such subjects Barbour¹¹⁸ has shown also that ether anesthesia, as well as morphine narcosis, is accompanied by a decrease in the water content of the brain The brain edema found at autopsy in cases of nephritic uremia status epilepticus and eclampsia in pregnant women is well known The work of Gamble,¹¹⁹ Fay,¹²⁰ the author,¹²¹ and others has demonstrated that a deficit in the body water tends to favor cessation of convulsions in epilepsy, while a positive water balance increases the convulsive tendency That associated disturbances in the mineral balance of the brain cells may be of importance in this connection is indicated by the more recent experimental studies of the author and his coworkers⁶⁴ ¹²² Like many of the other problems of water metabolism, however that concerning the precise relationship of tissue hydration to convulsive phenomena is greatly involved and will undoubtedly require far more extensive scientific investigation for its ultimate solution

In the present hurried review we have been able merely to sketch the vague outlines of the field of water metabolism in relationship to clinical medicine Nevertheless, it may suffice to stimulate additional interest in a comparatively neglected phase of practical physiology, which holds unusual promise for the future investigator

REFERENCES

- 1 Bernard, Claude *Leçons sur les Phénomènes de la Vie* Vol. I Paris, 1878
- 2 Cannon, W. B. *The Wisdom of the Body* New York 1931. W. W. Norton Company
- 3 Armstrong, H. E. *Proc. Roy. Soc.* 103A 610, 1923
- 4 Stewart, G. W. *Physic. Rev.* 37 9 1931
- 5 Henderson, L. J. *The Fitness of the Environment* New York, 1913, Macmillan Company
- 6 Matthews, W. P. *Physiological Chemistry* William Wood and Company ed. 3 1920
- 7 Volkmann, A. W. *Berichte u. d. Verhandl. d. Sachs. Gesellsch. d. Wissensch.* 26 202, 1874
- 8 Gamble, J. L. *New England J. M.* 201 909 1929
- 9 Engels, W. *Arch. f. exper. Pn্থ u. Pharm.* 51 346 1904.
- 10 Gortner, R. A. *Outlines of Biochemistry* New York 1929 John Wiley and Sons.
- 11 Balcar, J. O., Sansum, W. D., and Woodyatt, R. T. *Arch. Int. Med.* 24 116 1919
- 12 Gortner, R. A. *Trans. Faraday Soc.* 26 678 1930
- 13 Kudo, T. *J. Exper. Zool.* 33 435 1921
- 14 Rubner, M. *Sitzungsber. Preuss. Akad. Wissenschaft* 24 253 1923
- 15 Jackson, C. M., and Smith, V. D. E. *Am. J. Physiol.* 97 146 1931
- 16 Babcock, S. M. *Univ. Wisc. Agric. Exper. Sta., Res. Bull. No.* 22 1912.
- 17 Cathcart, E. P. *Glasgow M. J.* 108 1, 1926
- 18 Soderstrom, G. F., and DeBois, E. F. *Arch. Int. Med.* 19 931 1917
- 19 Benedict, F. G. and Root, H. F. *Arch. Int. Med.* 38 21 1906.
- 20 Johnston, M. W., and Newburgh, L. H. *J. Clin. Investigation* 8 147 1930
- 21 Levine, S. Z., Kelly, M. and Wilson, J. R. *Am. J. Dis. Child.* 39 911, 1930
- 22 Manchester, R. C. *Husted, Clara and McQuarrie Irvine* *J. Nutrition* 4 39 1931
- 23 Barbour, H. G., Loomis, N. M., Frankman, R. W. and Warner, J. H. *J. Physiol.* 59 300 1924.
- 24 Moss, K. N. *Proc. Roy. Soc. London* 95 181, 1923
- 25 Marriott, W. McKim *Am. J. Dis. Child.* 20 461 1920
- 26a. Gamble, J. L. and McIver, M. A. *J. Exper. Med.* 48 837 1928
- 26b. Gamble, J. L. *J. Exper. Med.* 48 859, 1928
- 27 Gamble, J. L., Putnam, M. C. and McKhann, C. F. *Am. J. Physiol.* 88 571 1929
- 28 McQuarrie Irvine, and Adolph, E. F.: *Whitehouse Conf. Report Part III* Sec. 1 page 301, 1932.
- 29 Cannon, W. B. *Bodily Changes in Pain, Hunger, Fear and Rage*, New York ed. 2 1929 D. Appleton and Company
- 30a. Marx, H. *Klin. Wchnschr.* 4 2330 1925
- 30b. Marx, H., and Mohr, W. *Arch. Exper. Pn্থ Pharm.* 123 205 1927
- 31 Richards, A. N. *Am. J. M. Sc.* 163 1 1927
- 32 Bykow, R. M. and Berkman, A. *Compt. rend. Acad. Sci. (Paris)* 185 1214 1927
- 33 Marx, H. *Klin. Wchnschr.* 10 64 1931
- 34 Marx, H. *Klin. Wchnschr.* 5 9° 1926
- 35 Weir, J. F., Larson, E. E., Rowntree, L. G. *Arch. Int. Med.* 29 306 1922
- 36 Snell, A. M., and Rowntree, L. G. *Endocrinology* 11 209 1927
- 37 Miller, J. L., and Williams, J. L. *Am. J. Med. Sc.* 161 827 1921
- 38 Harding, V. J. and Harris, L. J. *Tr. Roy. Soc. Canada* 24 101 1930
- 39 Rowntree, L. G. *J. Pharm. Exper. Therap.* 29 135 1926
- 40 Smyth, F. C., Callahan, W., and Phatak, N. M. *J. Clin. Invest.* 12 33 1913.
- 41 Lamson, P. D., and Roca, J. *J. Pharm. and Exper. Therap.* 17 481 1921
- 42 Plek, E. P.: *Harvey Lecture* New York 1929 1930
- 43 Leiter, L. *Medicine* 10 135 1931
- 44 Landis, E. M. *Yale J. Biol. and Med.* 5 201 1933.
- 45 Starling, E. H. *J. Physiol.* 19 312 1896
- 46 Muntwyler, E., Wav, C. T., Binns, D. and Myers, V. C. *J. Clin. Investigation* 12 495 1933
- 47 Moore, N. S., and Van Slyke, D. D. *J. Clin. Investigation* 8 337, 1930

- 48 Schade, H Wasserstoffwechsel Oppenheimer's Handb der Biochem, ed 2, Jena, p 175, 1925
- 49 Fenn, W O Proc. Am Phys Soc 49th Annual Meeting, Cincinnati, 1933
- 50 Hald, J A, Rauth, J W, Larkin, J, and Wright, P Am J Physiol 80 631, 1927
- 51 Weech, A. A, and Lang, S M. J Clin. Investigation 10 869, 1931
- 52 Degkwitz, R Klin. Wchnschr 9 2336, 1930
- 53 Dahmlos, J, and Solé, A Biochem. Ztschr 227 401, 1930
- 54 Haustein, F Arch f. Kinderh 86 33, 1928
- 55 Magnus, R, and Schafer, E A. J Physiol 27 1901
- 56 Von den Velden, R Berlin Klin. Wchnschr 50 1156, 1913
- 57a. Starling, E H, and Verney, E B Pflüger's Arch ges Physiol 205 47, 1924.
- 57b Verney, E B The Lancet 216 539, 1929
- 58 Starling, E H, and Verney, E B Proc Roy Soc B 97 321, 1925
- 59 Motzfeldt, K J Exper Med. 25 153, 1917
- 60 Blumgart, H L Arch Int Med. 29 508, 1922
- 61 McFarlane, A. J Pharm and Exper Therap 28 177, 1926
- 62 McQuarrie, Irvine and Peeler, D B J Clin Investigation 10 915, 1931
- 63 Thompson, W H, Ziegler, M, and McQuarrie, I Proc Soc. Exper Biol and Med 30 16, 1932
- 64 Richards, A. N, and Plant, O H Am J Physiol 59 191, 1922
- 65 Gehring, E M Physiol Rev 6 62, 1926
- 66 Marshall, E K Personal communication
- 67 Adolph, E F, and Ericson, G Am. J Physiol 79 377, 1927
- 68 Ponrowsky, N, and Ischannna, W Proc. XIIIth Internat Physiological Congress, Boston, 1929
- 69 Buschke, A Arch exper Path u Pharm 136 63, 1928
- 70 Stehle, R L Am. J Physiol 79 289, 1927
- 71 Barbour, H G Yale J Biol and Med 4 797, 1932
- 72 Glass, A. Arch exper Path u. Pharm 136 72, 1928
- 73 Janssen, S Arch. exper Path u Pharm 135 1, 1928
- 74 Hoff, H., and Potzl, O Ztschr ges Neurol u Psychiat 124 200, 1930
- 75 Oehme, C, and Oehme, A Klin Wchnschr 2 1, 1923
- 76 Marx, H Deutsches Arch f Klin. Med 158 149, 1928
- 77 Pines, L Deutsche Ztschr f Nervenh 107 178, 1928
- 78 Greving, R Deutsche Ztschr f Nervenh. 89 179, 1926
- 79 Camus, J, and Roussy, G Compt rend Soc de biol 83 764, 1920
- 80 Aschner, B Munchen. med Wchnschr 1 81, 1917
- 81 Bailey, P, and Bremer, F Arch Int. Med 28 773, 1921
- 82 Houssey, B A, and Hug, J Compt rend. soc. de biol. 89 51, 1923
- 83 Cushing, H, and Goetsch, E Am J Physiol 27 60, 1910
- 84 Hoff, H, and Werner, A. Arch f exper Path u Pharm. 133 84, 1928
- 85 Karplus, I. P, and Peczenik, O Arch ges Physiol 225 654, 1930
- 86 Cushing, Harvey Pituitary Body, Hypothalamus and Parasympathetic Nervous System. Charles C Thomas Co, Springfield, Illinois, 1932
- 87 Bourquin, Helen Am J Physiol 85 354, 1928
- 88 Olivet, J Jahresk f Arztl. Fortbild 21 34, 1930
- 89 Trendelenburg, P Arch Exper Path u Pharm 114 255, 1926
- 90 Teel, H M J A M A 93 760, 1929
- 91 Hann, F Frankf Z f Path 21 337, 1918
- 92 Glaubach, G, and Molitor, H Wien. klin Wchnschr 42 1437, 1929
- 93 Porges, J Wien. klin Wchnschr 40 1640, 1927
- 94 Grossmann, O Wien. klin Wchnschr 41 450, 1928
- 95 Lampe, W Naunyn-Schmeideberg, Arch Exp Path u Pharm 119 83, 1926
- 96 Owen, S E, and Ivy, A C Am J Physiol 97 276, 1931
- 97 Eppinger, H Zur Pathologie und Therapie des menschlichen Odems. Julius Springer, Berlin, 1917
- 98 Epstein, E Z Arch exper Path u Pharm 142 214, 1929
- 99 Mason, E H Canad M A J 16 538, 1926
- 100 Meakins, J C J A M A 89 149, 1927
- 101 McCann, W S J A M A 90 249, 1928
- 102 Reitzel, R J, and Stone, C J J A M A 91 1288, 1928

- 103 Baar, H Ztschr Kinderheilk. 46 502, 1928
- 104 Ellis, Max M Blochem. J 22 937, 1928
- 105 Drabkin, D L., and Shilkret Am. J Physiol. 83 141, 1921
- 106 Klein O Klin. Wchnschr 5 2304 1920
- 107 Schiff E. and Choremia, C Jahrb Kinderh. 114 42, 1926
- 108 Swingle W W., and Pfiffner, J J Proc. Am. Physiol. Soc. 40th Meeting Cincinnati, 1933
- 109 Silvette, H. Proc Am. Physiol. Soc. 40th Annual Meeting Cincinnati, 1933
- 110 Barbour H G Physiol. Rev 1 205 1921
- 111 Underhill, F P, und Ringer M J A M. A 75 1531 1920
- 112 Sandelowsky J Deutsch Arch f klin. Med. 96 445, 1909
- 113 Wilder T S and Drake T G H J Clin. Investigation 7 353 1929
- 114 Sunderman, F W and Austin J H Am J M Sc. 179 167 1930
- 115 Rackemann, F M. Longcope W T, and Peters, J P Trans. Assoc. Am. Physicians 31 215 1916
- 116 Rubin, M L., and Kellett, C E. Bull Johns Hopkins Hosp 49 170 1931
- 117 Barbour H. G., Russell, B E. Flowers, S. H., Dunham, E. S. and Hunter L G Am. J Physiol. 90 2, 1929
- 118 Barbour, H G: Science 73 346, 1931
- 119 Gamble J L: Arch. Neurol. and Psychiat 23 915, 1930
- 120 Fav Temple Am J Psychiat 8 783 1929
- 121 McQuarrie Irvine Am J Dis. Child. 38 451 1929
- 122 McQuarrie, Irvine, Manchester R C., and Husted Clara Am. J Dis Child 43 1510, 1932.

- 48 Sehade, H Wasserstoffwechsel Oppenheimer's Handb der Biochem, ed 2, Jena, p 175, 1925
- 49 Fenn, W O Proc. Am Phys Soc 49th Annual Meeting, Cincinnati, 1933
- 50 Haldi, J A, Rauth, J W, Larkin, J, and Wright, P Am J Physiol 80 631, 1927
- 51 Weech, A A., and Ling, S M. J Clin Investigation 10 869, 1931
- 52 Degkwitz, R. Klin. Wehnschr 9 2336, 1930
- 53 Dahmlos, J, and Solé, A Biochem Ztschr 227 401, 1930
- 54 Hausteim, F Arch f Kinderh 86 33, 1928
- 55 Magnus, R, and Schafer, E A J Physiol 27 1901
- 56 Von den Velden, R Berlin Klin. Wehnschr 50 1156, 1913
- 57a. Starling, E H, and Verney, E B Pfluger's Arch ges Physiol 205 47, 1924.
- 57b Verney, E B The Lancet 216 539, 1929
- 58 Starling, E H, and Verney, E B Proc Roy Soc B 97 321, 1925
- 59 Motzfeldt, K. J Exper Med. 25 153, 1917
- 60 Blumgart, H L Arch Int. Med 29 508, 1922
- 61 McFarlane, A J Pharm and Exper Therap 28 177, 1926
- 62 McQuarrie, Irvine and Peeler, D B J Clin Investigation 10 915, 1931
- 63 Thompson, W H, Ziegler, M, and McQuarrie, I Proc. Soc. Exper Biol and Med 30 16, 1932
- 64 Richards, A N, and Plant, O H Am J Physiol. 59 191, 1922
- 65 Geilung, E M Physiol Rev 6 62, 1926
- 66 Marshall, E K Personal communication
- 67 Adolph, E F, and Ericson, G Am J Physiol 79 377, 1927
- 68 Pomrowsky, N, and Ischumina, W Proc XIIIth Internat Physiological Congress, Boston, 1929
- 69 Buschke, A Arch exper Pathl u Pharm 136 63, 1928
- 70 Stehle, B L Am J Physiol 79 289, 1927
- 71 Barbour, H G Yale J Biol and Med 4 797, 1932
- 72 Glass, A Arch exper Pathl n Pharm 136 72, 1928
- 73 Jaussen, S Arch exper Pathl n Pharm 135 1, 1928
- 74 Hoff, H, and Potzl, O Ztschr ges Neurol u Psychiat 124 200, 1930
- 75 Oehme, C, and Oehme, A Klin Wehnschr 2 1, 1923
- 76 Marx, H Deutsches Arch f Klin. Med 158 149, 1928
- 77 Pines, L Deutsche Ztschr f Nerven 107 178, 1928
- 78 Greving, R. Deutsche Ztschr f Nerven 89 179, 1926
- 79 Camus, J, and Roussy, G Compt rend Soc. de biol 83 764, 1920
- 80 Aschner, B Munchen med Wehnschr 1 81, 1917
- 81 Bailey, P, and Bremer, F Arch Int. Med 28 773, 1921
- 82 Houssay, B A, and Hug, J Compt rend soc de biol 89 51, 1923
- 83 Cushing, H, and Goetsch, E Am J Physiol 27 60, 1910
- 84 Hoff, H, and Wermer, A Arch f exper Pathl u Pharm 133 84, 1928
- 85 Karplus, I P, and Peczenik, O Arch ges Physiol 225 654, 1930
- 86 Cushing, Harvey Pituitary Body, Hypothalamus and Parasympathetic Nervous System. Charles C Thomas Co, Springfield, Illinois, 1932
- 87 Bourquin, Helen Am J Physiol 85 354, 1928
- 88 Ohvet, J Jahressk f Arztl Fortbild 21 34, 1930
- 89 Trendelenburg, P Arch Exper Pathl u Pharm 114 255, 1926
- 90 Teel, H M J A M A 93 760, 1929
- 91 Hann, F Frankf Z f Path 21 337, 1918
- 92 Glanbaech, G, and Molitor, H Wien. klin Wehnschr 42 1437, 1929
- 93 Porges, J Wien. klin Wehnschr 40 1640, 1927
- 94 Grossmann, O Wien klin Wehnschr 41 450, 1928
- 95 Lampe, W Naunyn Schmiedeberg, Arch Exp Pathol u Pharm 119 83, 1926
- 96 Owen, S E, and Ivy, A C Am J Physiol 97 276, 1931
- 97 Eppinger, H Zur Pathologie und Therapie des menschlichen Odems Julius Springer, Berlin, 1917
- 98 Epstein, E Z Arch exper Pathl n Pharm 142 214, 1929
- 99 Mason, E H Canad M A J 16 538, 1926
- 100 Meakins, J C J A M A 89 149, 1927
- 101 McCann, W S J A M A 90 249, 1928
- 102 Reitzel, R J, and Stone, C J J A M A. 91 1288, 1928

it is recalled that successful cases are reported with far more frequency than those that succumb to the disease with or without operation. The careful scrutiny of the reports of a large number of hospitals for children would be the only basis for a rational deduction.

There seems to be little or no available data concerning many features of the etiology, such as the race, habits, climate, food or hereditary factors. When one thinks of the great variety of foods used by children of this country, and the contrast in living conditions, it would seem that if diet enters into the cause of ulcer it should be apparent after a careful survey. The reported cases do not suggest such a relation. In these days of the cafeteria and the delicatessen it would seem that ulcer would be the logical result of the indiscriminate barrage to which the gastrointestinal tract is subjected, if food plays any part in the etiology of ulcer. In the absence of any known etiology most writers on this subject believe the cause is the same as in the adult. This seems to be another way of saying we do not know. We can surely eliminate alcohol, tobacco and financial worries among the causes in children.

The ulcers have about the same anatomical distribution as in the adult, namely, on the lesser curvature near the pylorus and on the anterior wall of the duodenum. This will apply to 90 per cent of the cases. The ulcers go on to perforation or may heal and obstruct the pylorus by the cicatrix. No case of carcinoma which had its origin in a recognized ulcer has been reported in a child.

The symptoms are somewhat vague, except in the cases of perforation, and in those cases they have the symptomatology of peritonitis. If a careful history is obtained it will be noted in the majority of cases that the child has had some dyspepsia over a period of months. Usually the pain has been too mild to attract attention and at other times it has been cramplike. The relation to food and remission of symptoms have not been prominent. It is not unlikely that the appendix has been removed during one of the attacks but without relief of the dyspepsia. The outstanding symptom, if present, and it is present in 40 per cent of the cases is the vomiting of blood, or blood in the stools. This one symptom means more than all the others combined and as associated with dyspepsia should be the incentive for as thorough an examination as we would give the older patient. Other symptoms which have been noted are vomiting, hunger pain, epigastric pain, loss of weight, anemia, constipation and underdevelopment. These symptoms are so common to childhood that they lose their diagnostic significance. Children are so prone to vomit and suffer cramps that these symptoms ordinarily of prime importance in any abdominal complaint in an adult are generally dismissed with a dose of castor oil and an indictment of the previous meal. Only the most painstaking exams

tion can elicit the complaints from an intelligent child that the man or woman would disclose with cheerful garrulity

It is so exceptional that the diagnosis of chronic ulcer is correctly made that one hesitates even to suggest it. One essential is to realize that chronic peptic ulcer in children is possible. With this fact in mind, chronic dyspepsia in a child should certainly excite our suspicions and demand the use of the x-ray. Few roentgenologists are willing to go further in diagnosis of chronic ulcer than to state that an organic lesion is present in the prepyloric region or the duodenum, unless a typical crater is present. Hematemesis or melena, in the absence of a known cause, points strongly to the presence of an ulcer, and with a roentgenogram showing an organic lesion near the pylorus, the diagnosis is almost conclusive.

The treatment offers very much and should be medical primarily, unless confronted with a surgical emergency. Too few cases have been reported in which the medical treatment has been checked before and after with the x-ray. The diagnosis could scarcely be in doubt in some cases that have responded promptly to dietary measures and remained well over a period of years. The Sippey treatment has been generally used. Surgery is necessary in the perforation, the pyloric obstruction, and in the case that does not respond to long and careful medical measures. When an operation is demanded, except for perforation, a plastic operation on the pylorus, such as the Mayo, Judd, or Finney should be the one of choice, and the posterior gastroenterostomy reserved for that type in which the former operations are inappropriate or impossible. We wish to report two cases.

CASE 1—Miss D. F. of North Carolina, fifteen years old, referred by Dr. William Gerry Morgan, from whose records these notes were made.

Family History—Parents living and well. Two brothers died of accidents. Other brothers and sisters (four) in good health.

Past History—She has had the milder diseases of childhood. Since the age of six has had "bowel trouble," and at this age had her first hemorrhage from the bowels. She has never been robust since. Her tonsils were removed a year later, and at the age of thirteen an appendectomy was done.

Present Illness—Beginning at the age of six, with her first hemorrhage, she has suffered with pain in the region of the gallbladder or pylorus, and constipation has been pronounced. She has been on a diet which contains much roughage, but with out relief to either the pain or constipation. There have been intervals of relief from the pain, and then vomiting and pain would return, lasting periods of three weeks approximately. Since February, 1932, she has had less relief and on seven different occasions macroscopic blood has appeared in the stools.

Physical Examination—Weight 101½ pounds, height 64¼ inches. Skin clear and of good color. Respiratory murmur clear and breezy, no rales, expansion good. Heart sounds were regular, clear, rate 72 per minute—apex beat not displaced. Liver dullness normal. Gallbladder could not be felt and no tenderness elicited.

Abdomen—Pannus spare, belly flat, spine prominent, splenic dullness normal. Old well healed appendiceal scar. Abdominal reflexes exaggerated. Recti of good tone. Only tenderness to be noted is at the site of the appendix scar.

Gastric Analysis—Free HCl 56, combined acidity 11 total acidity 66

Blood Examination—R.B.C. 4,400,000, W.B.C. 7500 Hg 79, 48 polymorpho nuclears, 46 lymphocytes 4 eosinophiles 1 basophile, 1 large mononuclear. Marked anemolia. Coag time $2\frac{1}{4}$ minutes.

The examination of the urine showed no abnormal constituents and the stool was negative for blood. B.M.R., 12 per cent, 17 per cent, 5 per cent on three different occasions. The x ray examination is reported as follows

'The chest is negative. The stomach shows marked reduplication of the mucosa. The rugae are very prominent throughout the entire stomach and the same condition also causes deformity of the duodenal cap. The appearance is that of a baggy redundant mucosa and strongly suggests polyposis in the duodenum. It is noted that at the 24 hour period the stomach is filled with some opaque material probably some bismuth or other opaque material taken by the patient. The caecum is dilated but is otherwise normal. The entire colon is spastic but shows no other abnormality. There is no evidence of periapical disease of the teeth. Re-examination one week later of the stomach and duodenum after the administration of belladonna shows the same appearance as at the previous examination. There is marked redundancy of the mucosa throughout the entire stomach and the deformity of the duodenal cap is exactly the same. Diagnosis—Gastric polyposis.'

Operation.—On June 3 1932, the abdomen was explored through an upper right rectus incision. The stomach wall was markedly hypertrophied. An active ulcer, about 1 cm in diameter was found on the anterior wall of the first portion of the duodenum. It was excised, and a posterior gastroenterostomy was done. The fixation of the duodenum made a pyloroplasty difficult to execute and it was not attempted. No other abnormality was found in the abdomen.

The patient's recovery was without incident and she has remained well.

CASE 2—M. S., female, seven years old. This patient was seen in consultation with Dr Robert A. Bler, who kindly furnished me data of which the following is an abstract:

Family History—Father Filipino mother, Greek, patient born in France

Past History—Early past history irrelevant except she has been somewhat under nourished and underdeveloped all her life. In January 1932 she was first seen and a diagnosis of juvenile pulmonary tuberculosis was made. She was seen at infrequent intervals until June 6 when x ray examination reported lungs essentially clear

Present Illness.—July 21 1932 patient reported complaining of pain in the abdomen during the previous two days, following some indiscretion in diet. The physical examination was negative. In November 1932 patient's mother reported that the child had tarry stools in two successive days. Pain and fever were absent. The physical examination at this time was reported as follows

The patient is a small swarthy female seven years of age. Outside her under weight and marked anemic appearance the physical examination was essentially negative. The examination of the abdomen was carefully made but elicited no positive findings.

The Wassermann was reported negative a few days later

The stool showed blood in large quantities. The mother stated upon closer questioning that a tarry stool was noted about one year previously, but she failed to mention it until this time. The following day two more bloody stools were reported and patient was admitted to the Children's Hospital and a blood examination made at that time was reported as follows. Hemoglobin 33 per cent (Newcomer), erythrocytes 2,550,000 leucocytes 8,200 lymphocytes, 30, polymorphonuclears, 70 lobulated, 64, band forms 4 young forms, 2.

Tuberculin test negative

Urine contained albumin upon the first examination but three days later albumin was absent

A few days after admission to the hospital the child complained of mild pain in the abdomen

The x-ray examination of the gastrointestinal tract, made at this time, reads as follows "The esophagus is normal. There is a constant deformity at the pylorus and at the base of the duodenal cap with approximately 10 per cent six hour residue. Appearance is that of an ulcerative lesion at the pylorus. Appendix normal. Colon normal throughout."

The patient was placed on a diet of the Sippy type and at last accounts was making excellent progress, without recurrence of blood in the stools. Operation was not indicated, in our opinion.

This presents almost a typical case of duodenal ulcer in a child, and if the bloody stools and x-ray examination could be eliminated from the history, the diagnosis would not be possible. This emphasizes the importance of melena as a symptom and the necessity of x-ray examinations in suspected cases.

COMMENT

That a child may have a chronic peptic ulcer must be an accepted fact, and the few cases reported (excluding those attended with perforation) indicate that a better understanding of the symptomatology is necessary if the disease is to be recognized in a fair percentage of cases before a serious complication discloses the real nature of the disease. There has not come to our notice any extended study of dyspepsia in childhood, having in mind the possibility of peptic ulcer, that included such examinations usually employed in the adult. We are convinced that such an investigation, no doubt beset with many difficulties, would have its own reward in setting up a clinical concept of ulcer in children and permit a better classification of diseases that are obviously mislabelled.

There is hardly a surgeon of wide experience who has not removed an appendix from a child in which the pathology found did not explain the symptoms. The recovery of the patient is his chief source of comfort as he knows only too well that the diagnosis was missed. That his consultants were equally wrong adds a little balm. It is not unlikely that some of these cases are peptic ulcers, as in one case herein reported.

Is it not possible that if the subject of dyspepsia in children were given the same intensive consideration bestowed on many other human ills, a group of symptoms would be found that makes the recognition of the disease possible in its early stages? At the present time no such group of symptoms, no x-ray studies, no pathological set-up is available, based on a large number of cases. The need is apparent and no doubt will be met.

REFERENCES

- 1 Sterns, M. A., Perkins, E. L., and Nesset, N. J. Jour. Lancet 49: 402, 1929
- 2 Proctor, O. S. Surg., Gynec. and Obst. 41: 63, 1925
- 3 Foshie, I. C. J. A. M. A. 99: 16, 1932

THE SERUM ALBUMIN AND GLOBULIN OF NEWBORN, PREMATURE AND NORMAL INFANTS

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THE concentration of serum proteins has been studied for years. However, most of the pediatric literature concerns determinations by physical methods (particularly by refractometry) which give large and uncertain errors. Recent work emphasizes the different functions of globulin and albumin. The physical methods for determining the albumin and globulin are even more erroneous than similar methods for estimating the total protein. Although the chemical methods occasionally give false results in the separation of the fractions of serum proteins, a sufficiently true picture can be obtained in this way to warrant an examination of infants' serum. This paper reports the total protein, albumin and globulin concentrations of newborn, normal infants from the fourth to the eighth month and premature infants. In addition a few determinations in pathologic conditions are listed. The data form a standard for evaluating protein concentrations during the first year of life.

LITERATURE

Mello-Leitao¹ reviews the literature on serum proteins in infants estimated by refractometry. This work shows that the serum proteins are lower in young infants than in adults and that the proteins increase gradually during the first eighteen months of life. Marriott² and others found the serum protein low in undernutrition and marasmus. Mello-Leitao obtained high values in congenital syphilis.

Webb³ using the colorimetric method of Wu which gives slightly high values for albumin found for young babies the following values: total protein 6.04 per cent, albumin 4.41 per cent and globulin 1.63 per cent. The rise in the total protein with age was shown to consist of an increase of proportionately more globulin than albumin. Simple undernutrition gave essentially normal values. No striking change with infections was found except in bone tuberculosis, osteomyelitis and infections accompanied by albuminuria. Infections of the bones were quite regularly accompanied by increase in globulin while albuminuria was accompanied by decrease in albumin and sometimes by an increase in globulin.

The association of the precipitin reaction with the globulin has led to examination of the effect of infections on this fraction of serum protein. The occurrence of *colon bacillus septicaemia* in calves which receive no colostrum was shown by Smith and Little⁴ and Howe⁵ to be accompanied by a failure to obtain globulin.

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Inspection of the chart reveals that the total protein is widely scattered in each group so that there is considerable overlapping of single determinations of the various groups. The differences between the averages of the various groups \pm the "probable error" of the differences are tabulated in Table I. Since a difference which is three times the "probable error" of the difference can only occur through chance sampling in about 5 per cent of the cases, such a difference

TABLE I

DIFFERENCE BETWEEN AVERAGE CONCENTRATION \pm "PROBABLE ERROR" OF DIFFERENCE

	PER CENT PROTEIN	PER CENT ALBUMIN	PER CENT GLOBULIN	$\frac{A}{G}$
Normal—Newborn	$+0.76 \pm 0.11$	$+0.55 \pm 0.09$	$+0.23 \pm 0.09$	-0.02 ± 0.10
Newborn—Premature	$+0.58 \pm 0.12$	$+0.15 \pm 0.08$	$+0.60 \pm 0.12$	-0.73 ± 0.09
Normal—Premature	$+1.34 \pm 0.10$	$+0.70 \pm 0.09$	$+0.83 \pm 0.11$	-0.75 ± 0.09

may be regarded as significant. This test of significance confirms the impression given by the chart that the concentration of the total protein is greater in the older normal infants than in the newborn and greater in the latter than in the premature. Although the average albumin of the premature infants is slightly lower than that of the newborns, this difference cannot be regarded as statistically signifi-

TABLE II

POSTMORTEM BLOODS IN FETUSES

WT. GM.	PER CENT PROTEIN	PER CENT ALBUMIN	PER CENT GLOBULIN	$\frac{A}{G}$
650	4.02	2.63	1.39	2.0
780	5.19	4.04	1.15	3.5
850	3.50	1.54	1.96	0.9
1500	5.88	3.65	1.73	2.2
1400	3.58	2.51	1.07	2.3
1200	3.89	1.65	2.24	0.7
1500	4.10	3.13	0.97	3.2
1025	3.76	2.57	1.19	3.1
1900	3.32	2.31	1.01	2.3

cant. However, the albumin of older normal infants is definitely higher than that of the other two groups. The globulin is also higher in the older normal infants than in the other two groups and higher in the newborns than in the premature.

The use of the albumin-globulin ratio is not altogether satisfactory but is so generally employed that these values were computed. The ratio depends on the accuracy of the determinations. Since globulin is determined by difference, any error in the albumin determination becomes greatly magnified in the albumin-globulin ratio. For this reason conclusions should only be drawn from changes in albumin or globulin concentration. Our data indicate that the proportion of globulin is reduced in premature infants.

Since the finding of low globulin in premature infants might depend on failure of globulin to develop till late in fetal life, several specimens of fetal blood were examined. In these cases for various reasons, labor occurred early but the fetus died late during labor or within one or two hours after birth. The blood was taken immediately after death. The results are given in Table II. We do not wish to draw conclusions concerning the concentration of albumin or globulin during fetal life from these figures, but merely point out that they do not indicate any decrease in the proportion of globulin in the serum of fairly small fetuses.

Since certain infections are known to raise the globulin, a study of the serums of babies with infection should reveal a failure of infants to react in the usual fashion. Table III gives results in various conditions. In the last four cases, the patients were prematurely born.

TABLE III
SERUM PROTEINS IN INFANTS WITH INFECTIONS

CASE NUMBER	AGE DAYS	DIAGNOSIS	DAYS ILL	PROT	ALB.	GLOB.	$\frac{A}{G}$
1	330	Measles, Pneumonia	14	6.16	3.0	2.52	1.4
2	210	Syphilis	210	7.08	4.08	3.00	1.4
3	250	Scurvy	607	6.39	3.48	2.91	1.2
4	150	Rickets, Eczema	907	6.74	3.41	3.38	1.0
5	250	Otitis Media	90	7.75	3.78	3.97	1.0
6	880	Pertussis Pneumonia	30	6.68	4.10	2.02	1.6
7	65	Undernutrition	7	5.34	3.01	1.78	2.1
8	120	Polymycolitis	16	5.84	3.05	1.20	1.8
9	210	Mental Deficiency	210	7.46	5.78	1.73	3.3
10	100	Malnutrition Diarrhea	7	5.74	4.14	1.60	2.6
11	180	Cerebral Palsy Unexplained Fever	28	6.22	3.9	2.27	1.7
12	270	Rickets Tetany Rhinorrhea	36	6.80	6.14	1.66	3.1
13	77	Microcephalus Otitis Media	14	6.41	4.03	1.78	2.6
14	180	Otitis Media Convulsions	14	6.01	4.31	2.60	1.7
15	180	Pneumonia	5	5.30	2.92	2.47	2.0
16	00	Syphilis	60	5.72	2.03	3.09	0.9
17	180	Otitis Media Diarrhea	7	6.32	4.18	2.14	2.0
18	200	Chronic Pneumonia	36	6.57	3.87	2.70	1.4
18	210	Chronic Pneumonia	40	6.95	4.43	2.52	1.8
19	70	Pneumonia	76	6.20	4.38	1.93	2.2
19	90	Recovered	66	6.71	4.7	2.24	1.9
20	330	Otitis Media	10	6.74	4.19	2.57	1.6
21	360	Dermatitis	30	6.22	2.56	3.66	0.7
22	7	Neonatal Sepsis	7	6.05	2.90	3.06	1.3
23	120	Diarrhea, Otitis Media	16	7.10	5.48	1.62	3.4
24	80	Diarrhea Otitis Media	14	5.60	3.28	3.32	0.7
25	25	Diarrhea	7	4.14	2.77	1.37	2.0

We may conclude that single determinations almost certainly represent a deviation from normal when they differ from the average of their group more than two standard deviations. Since these babies are of the age of the group of normal infants, they should be compared

to the average of this group. Applying this criterion six albumins are low. Cases 3, 4, 8, 15, 16, and 21. Case 21 was a peculiar unclassifiable skin disease resembling Leiner's dermatitis exfoliativa, and was the only one manifesting edema. Undernutrition probably played a part in reducing the albumin in the cases of scurvy, eczema, pneumonia, and syphilis. Case 9 (mental deficiency) probably showed a high albumin because of an unsuspected dehydration. The globulin was high in Cases 2, 3, 4, 5, 6, 18, and 21. The most striking elevations are in the patients with syphilis and skin infections.

Since opportunity to study premature infants with infection who are not also dehydrated does not occur often, such cases are few in our series. Cases 24 and 25 suggest that premature infants are apt to develop low albumin with diarrhea and infection. Cases 20 and 24 demonstrate that premature infants can produce a high globulin content in their serums.

DISCUSSION

The average values for adults (Peters and Van Slyke¹⁹) is for men, protein 7.00 per cent, albumin 4.44 per cent, globulin 2.58 per cent and A/G ratio 1.72, for women, protein 7.02 per cent, albumin 4.35 per cent, globulin 2.68 per cent and A/G ratio 1.62. Plass and Mathews,²⁰ Oard and Peters²¹ and others have shown that a decrease in serum albumin occurs during pregnancy. Our data indicate that older normal babies have about the same albumin concentration as adult women, but slightly lower globulins. Thus the low proteins of infants is chiefly due to low globulins, though a reduction in albumin corresponding in magnitude to that occurring in pregnant women, is found in newborn infants. In this respect premature infants are like newborn infants, except that their globulin tends to be even lower.

The data on the premature infants showed no relation between the various protein constituents and the age, the birth weight, birth length and the weight at time of examination. The low albumin may be characteristic of small babies since none of these infants weighed over 2900 grams when the blood samples were taken. Six samples taken during the first thirteen days of life did not differ significantly from the group as a whole. The ages range from six to ninety days, but most of the examinations occurred between the twentieth and fortieth day after birth.

The work of Achard, Bariéty, and Codouris demonstrates that infants are born with about the same concentration of albumin as their mothers, but with definitely lower globulins. This fact suggests that albumin may diffuse across the placenta but apparently globulin behaves somewhat differently. The production of albumin is interfered with in severe undernutrition (Bruckman, D'Esopo and Peters,²² Frisch, Mendel and Peters,²³ Weech and Ling²⁴ and others). Our data indicate that albumin concentration is more constant than globulin

concentration. After depletion of serum proteins by plasmapheresis, globulin is regenerated more rapidly than albumin¹⁴. Globulin apparently increases greatly beyond its usual concentration in response to tissue injury¹⁰ and certain infections². Since babies during the first few months of life have suffered from few infections, these observations suggest that infants may have low concentrations of globulin largely due to absence of the stimuli which lead to globulin production in adults.

SUMMARY

The serum concentration of total protein, albumin and globulin was determined in 20 newborn infants, 14 normal infants, aged about five months, and 26 premature infants. Similar studies in full term and premature infants suffering from various diseases were made.

The total protein is decreased in all infants, the decrease being due chiefly to low globulin. The diminution in globulin is greatest in premature infants.

Postmortem serum of small fetuses shows essentially the same albumin globulin ratio as that of full term infants.

Both premature and normal infants may show an increase in globulin during infection.

It is suggested that the low globulin in infants may indicate the lack of the usual stimuli that give rise to globulin production in adults.

REFERENCES

- 1 Mello-Leitao. *Am. J. Dis. Child.* 11 214 1916
- 2 Marriott McKim. *Am. J. Dis. Child.* 20 401 1920
- 3 Webb C. H. *Am. J. Dis. Child.* 44 1-39 1923
- 4 Smith Theobald, and Little R. B.: *J. Exper. Med.* 36 181, 453 1921
- 5 Howe, P. E. *J. Exper. Med.* 39 313 1924
- 6 Achard C., Barletty, M., and Codounis A. *Compt. rend. Soc. de biol.* 102 984 1929
- 7 Starlinger W. *Deutsche med. Wchnschr.* 54 731, 1928
- 8 Rowe A. H. *Arch. Int. Med.* 18 455, 1916
- 9 Wiener H. J., and Wiener R. E. *Arch. Int. Med.* 48 236 1930
- 10 Hurwitz, S. H., and Meyer K. F. *J. Exper. Med.* 24 515 1916
- 11 Hurwitz, S. H. and Whipple G. H. II *J. Exper. Med.* 25 231 1917
- 12 Loeper, M. Ravier J. de Sile and Lepert M. *Compt. rend. Soc. de biol.* 101 423, 1929
- 13 Peters J. P., and Van Slyke D. D. *Quantitative Clinical Chemistry I* In Interpretations Baltimore 1931 Williams and Wilkins Co. p. 61
- 14 Kerr W. J. Hurwitz, S. H., and Whipple G. H. *Am. J. Physiol.* 47 336 340 349 1918
- Letter L. *Arch. Int. Med.* 48 1 1931
- Darrow D. C. Hopper E. B., and Cary M. K. *J. Clin. Invest.* 11 683 1932
- 15 Peters, J. P., and Van Slyke D. D. *Quantitative Clinical Chemistry II* Methods, Baltimore 1932 Williams and Wilkins Co. p. 691
- 16 Howe P. E. *J. Biol. Chem.* 57 241 1923
- 17 Weech A. A. Smelling C. E. and Goettlich, E. *J. Clin. Invest.* 12 197 1923
- 18 Butler A. M., and Montgomery H. *J. Biol. Chem.* 99 173 1933
- 19 Same as Ref. 13 p. 602.
- 20 Plass, F. D. and Mathews, C. W. *Am. J. Obst. & Gynec.* 12 840 1926
- 21 Oard H. C. and Peters J. P. *J. Biol. Chem.* 81 9 1929
- 22 Bruckman, F. S. D'Esopo L. M. and Peters, J. P. *J. Clin. Invest.* 8 517 1930
- 23 Frisch R. A. Mendel L. A., and Peters J. P. *J. Biol. Chem.* 84 107 1929
- 24 Weech, A. A., and Ling S. M. *J. Clin. Invest.* 10 869 1931

MANAGEMENT BY MECHANICAL RESPIRATOR OF POSTDIPHTHERITIC RESPIRATORY PARALYSIS

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THE clinical similarity of respiratory failure in late diphtheria and in certain forms of poliomyelitis is apparent to physicians familiar with the two diseases. Wilson¹ has emphasized that poliomyelitis can prevent efficient respiration through direct paralysis of the primary respiratory muscles, through interference with respiration in patients with pharyngeal paralysis in whom inspiration is continually interrupted by unswallowed secretions collecting around the glottis, and finally through a disturbance of the nerve centers in the medulla controlling respiration. Respiratory difficulty in any patient ill with poliomyelitis may be due to a single one of these factors or to a combination of two or more.

The striking difference between respiratory difficulty in poliomyelitis and in late diphtheria is that in infantile paralysis the cause is commonly of central origin, while in diphtheria the difficulty is chiefly concerned with paralysis of the diaphragm and of the intercostal muscles. In both conditions the factor of accumulated secretions following paralysis of the muscles of the pharynx is often important. The careful observations of Wilson have demonstrated that in poliomyelitis the response to management with the Drinker² respirator is much more favorable when the lesion is related to the cervical and dorsal cord, with resultant paralysis of the intercostal muscles and of the diaphragm, than when the involvement is primarily bulbar. Our own experience has been the same, and logically led to consideration of this method in the management of late respiratory paralysis in diphtheria.

Since 1927, 5057 cases of diphtheria have been admitted to the wards of the Herman Kiefer Hospital, Detroit. The number of deaths was 632, of which an appreciable number, eighty-seven, were due to the toxic effects of the infection and occurred within the first few days. Circulatory failure was by far the commonest cause of death, being responsible for no less than 415 fatalities. Among patients with the laryngeal form of diphtheria the commonest contributing cause of death was pneumonia, ninety-six cases, with suffocation from obstruction essentially uncommon. Septicemia, generalized suppurative peritonitis, nephritis, empyema thoracis and activated pulmonary tuberculosis were rare causes. Fatality in thirteen instances was due to respiratory insufficiency after paralysis,

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or about 2 per cent of all deaths. The condition is not frequent but when it does occur is of serious moment, in that of twenty-one patients with diaphragmatic and intercostal paralysis thirteen died, a case fatality of 61.9 per cent.

Paralysis of respiratory function in diphtheria is as a rule a late development. The condition is almost completely limited to patients with an original massive infection of the throat, where the membrane involves not only the fauces but extends into the nasopharyngeal vault and generally involves the palate and the uvula as well. The first paralysis to develop is ordinarily related to inhibition of function of the palate, and would seem to depend largely upon local absorption of toxins. It usually appears on the eighth to fourteenth day after onset. The paralysis next most commonly observed involves the muscles of the eye. At about this same time, the third week, a paralysis of the muscles of the larynx and of the pharynx may occur. By the fourth week the muscles of the extremities are likely to be involved and not uncommonly sensory disturbances are present, indicated by numbness, prickling and hyperesthesia of the extremities. Respiratory paralysis rarely develops other than in the wake of such a progression of paralysis.

In this group of patients the earliest onset of respiratory paralysis was on the twenty-seventh day, the latest on the fifty-sixth. The course of events in overwhelming faucial diphtheria is a severe toxemia lasting four to five days, followed almost invariably by severe circulatory disturbance on the eighth to sixteenth days. In those surviving this hazard paralysis of the muscles of respiration may be anticipated about the sixth week. The time of this reaction is so constant that trouble is looked for at about the thirty-fifth day in the hospital which corresponds to about the fortieth day of the disease. Our experience in the onset of respiratory paralysis is illustrated in Table I.

Since paralysis of respiratory function occurs only in late convalescence all deaths from diphtheria have been reviewed in regard to the day of the disease on which they occurred. Of the 632, only twenty-nine were after the twenty-first day. Of these thirteen were due to paralysis of the muscles of respiration, ten to circulatory failure and six were attributed to bronchopneumonia. Postdiphtheritic paralysis is thus the most common cause of death during convalescence.

TABLE I
DAY OF ONSET OF POSTDIPHTHERITIC RESPIRATORY PARALYSIS

DAY OF ONSET	CASES
21 - 2	1
28 - 34	3
35 - 41	11
42 - 48	5
49 - 55	0
56 - 62	1

Drinker in 1929 reported a mechanical apparatus for maintaining prolonged artificial respiration and gave a description of a fatal case of poliomyelitis treated by the method. Later³ he presented an analysis of additional cases, suggested the use of the apparatus in the orthopedic treatment of intercostal paralysis, and reported on its use in seventeen cases of gas poisoning, eight of alcoholic coma, five of drug poisoning, and one of drowning. Jackson⁴ has described the development of mechanical methods for prolonged respiration. Murphy⁵ and others reported a modification of the original Drinker apparatus designed for small children and infants, with an appliance for the administration of oxygen and carbon dioxide in the treatment of asphyxia of the newborn. Murphy, with C. K. Drinker and Philip Drinker,⁶ emphasized that respiratory paralysis in the presence of an exudative process in the lungs is likely to make but little progress when managed by the respirator. Reports on the method in poliomyelitis complete the literature.⁷ To these indications may now be added another, the application of the method to postdiphtheritic respiratory paralysis.

CASE 1.—Elizabeth K., aged eight years, became ill on December 1, 1931, with sore throat, fever, and headache. The next day the glands of the neck were swollen, she vomited twice and complained of constipation. A well marked discharge from both nasal passages was present on the third day and the swelling of the neck was exaggerated. She was not seen by a physician until late on the fourth day. He administered 10,000 units of antitoxin and sent the child to the hospital.

The temperature was then 102.4° F., the pulse rate was 120 and the respiratory rate 32. General physical examination indicated a child critically ill. There was a mucopurulent discharge from both nares. The neck was so swollen, because of enlargement of the cervical lymph nodes and the adjacent tissues, as to produce a rounded effect almost obliterating all markings and suggesting the possibility of parotitis. The tongue was markedly coated. The tonsils were so enlarged and swollen that they essentially met in the midline of the throat. A thick diphtheritic membrane covered the entire surfaces of both tonsils, all visible portions of the pharynx, the uvula and the soft palate. Both lung fields were clear. The heart borders were within normal limits. No murmurs were heard. The cardiac sounds were well preserved and the rhythm regular. The child was poorly nourished and pale. Sixty thousand units of diphtheria antitoxin were administered on the evening that the child came to the hospital, and an additional 40,000 units the following morning. On the sixth day of illness, the patient was clinically much worse, and the blood pressure was at the extremely low level of 72/48. The cardiac tones were softer and the heart rate more rapid.

On the fourteenth day the blood pressure dropped sharply to a level which long experience has shown to be compatible usually with no other than a fatal prognosis, the systolic pressure being 54 and the diastolic indeterminate. A marked gallop rhythm was present. For the next several days the child was listless, took nourishment and fluids poorly and barely seemed to live from day to day. Palatal paralysis was first noted on the twenty-first day and shortly thereafter paralysis of the muscles of the pharynx, accompanied by the collection of much mucus in the throat because of inability to swallow. Repeated aspiration was performed with a mechanical suction apparatus. On the twenty-fourth day the patient complained of blurring of vision, and within the next two or three days, of general hyperesthesia, particularly numbness and tingling of the extremities. By the thirty-seventh day the

paralysis of the throat had become so extensive as to necessitate feeding by nasal catheter. The circulatory condition was somewhat improved. Throughout the forty-second day the patient was fairly quiet but in the early evening became restless and cyanotic from insufficient oxygenation. At 10:30 p.m. the respiratory effort was of such degree that the patient could not be restrained. She continually tossed about and attempted to sit up. Paralysis of the intercostal muscles, which had been first noted three days previously was at this time so extreme that breathing was almost entirely abdominal. It was felt that exitus was imminent unless aid to respiration could be accomplished. During the course of transfer from her room to the mechanical respirator the child's struggle for air ceased and there was a gurgling shallow type of breathing indicative of complete exhaustion.

The child evidenced a remarkable change shortly after being placed in the respirator. Within an hour all restlessness had disappeared and she slept comfortably the remainder of the night. The color of the lips and nail beds improved. During the early hours of treatment a pressure of 18 to 20 mm. was used but the next morning this was reduced to 8 mm. with equally good effect. The following day the patient slept a goodly portion of the day although the machine was continuously in motion. Mucus continued to collect in the throat and was a troublesome factor which demanded repeated use of the aspirating apparatus. The following three or four days were uneventful. On the fifth day the child was out of the respirator twice for periods of six and ten minutes during which time respiration was fairly regular but rapid and somewhat shallow with movements of the chest exaggerated. After seven days the respirator was no longer required except for periods of exercise. Active respiration was much improved although the accumulation of mucus in the throat continued a matter of concern. Convalescence was progressive so that by the seventy-eighth day she was able to be up for the first time and on the eighty-fourth day was discharged from the hospital recovered.

CASE 2—John W. aged eighteen years became ill on April 3, 1932 with sore throat and fever of undetermined degree. The next day he complained of chilliness, of abdominal pain and vomited several times. Headache became a pronounced symptom. Swelling of the glands of the neck was first noticed on April 4. During the next two days his illness progressively became of greater moment although he was not seen by a physician until April 7, the fifth day of his illness.

The patient was admitted to the hospital in a critical clinical condition. The fever was 101.6 F., the pulse rate was 88 and the respiratory rate 26. The lips and nail beds were deeply cyanosed. The patient was rational, cooperative but markedly toxic. The swelling of the neck was not limited to the lymph nodes but involved the tissues about the glands, to give a periadenitis and edema of extreme degree. A gray white membrane covered both tonsils, extended upward to involve the nasopharynx and forward to completely cover the uvula, the entire soft palate and even part of the hard palate. The distribution of diphtheritic membrane and the severity of the general reaction were about as severe as may be seen in malignant diphtheria. The heart rate was slow but regular. The heart tones were ill defined and muscular. No murmurs were heard.

Antitoxin in the amount of 80,000 units was administered immediately with an additional 40,000 units the following day. The patient's condition was extremely precarious during the early days in the hospital, subsequently slowly improved and the mucous membranes of the pharynx were first entirely free from membrane on the eighth hospital day. The blood pressure which at the time of admission was 100 mm. Hg systolic and 70 diastolic dropped at this time to 82/50 and the heart tones were only of fair quality. On the fifteenth day the patient was very pale and the pulse rate had dropped to 52. There was every clinical evidence of myocarditis

with impending circulatory failure of diphtheria, and complaints of nausea and epigastric pain. The following day a gallop rhythm was well defined. The blood pressure was 75/40. The liver was tender and palpable. Palatal paralysis was noted. On the eighteenth day the quality of the heart sounds was somewhat improved, also the rhythm, and the blood pressure was slightly higher. Dating from that time there was well marked improvement, so that by the twenty fifth day the pulse rate was 80 and the blood pressure was 96/66. For the first time, however, he complained of difficulty in swallowing and this was accompanied by an irritative cough.

No distinct advance occurred in the paralysis of the muscles of the pharynx until the fortieth day, when the voice developed a marked nasal quality and the paralysis became so well defined that he had emesis of food through the mouth and nose. The quality of the pulse was not as satisfactory. He spent a restless night. Because of repeated emesis, nasal feeding was instituted. On the forty first day the respirations were irregular and somewhat shallow, although the pulse was stronger. The patient slept a great deal. He complained of blurred vision. In the course of the early afternoon respiratory effort became pronounced and at 4.45 he was placed in the Drinker respirator, cyanosis being then very definite and the respirations so labored as to be alarming. The pulse rate was 140, and the temperature had increased to 101° F. The paralysis of respiration was distinctly of the intercostal muscles, in that although the rate of respiration was rapid there was little movement of the chest. It was believed that bronchopneumonia was also present.

The pressure of the machine was maintained at 18 to 22 mm and the rate at 16 and later 32. At no time could the patient accommodate respiratory effort to the rhythm of the machine. He progressively became worse and death occurred at 10.05 P.M., essentially five hours later.

DISCUSSION

The clinical similarity between postdiphtheritic respiratory paralysis and that form of poliomyelitic paralysis reacting most favorably to management with the Drinker respirator indicated the probable value of the method in diphtheria. Our experience would suggest another worth-while use of the method in the field of communicable disease.

In criticism of the conduct of these two cases, we feel that the observation of Wilson applies pertinently here as in poliomyelitis, in that both patients might well have been given earlier advantage of the method. The patient who recovered was placed in the machine within minutes of an expected exitus, and the one whose illness terminated fatally might well have received material benefit by its use at least three days earlier. Our experience with this method in poliomyelitis had been discouraging, to such an extent that we hesitated to make use of it in diphtheria unless no other measure was possible. With the earlier types of apparatus it was difficult to provide ordinary symptomatic and hygienic care. This is not a criticism of the more recent models of the respirator.

If artificial respiration by this method is started at the first sign of difficulty it is believed that a greater proportion of recoveries will be noted among patients with postdiphtheritic paralysis than with any other of the conditions which may be treated by this method.

CONCLUSIONS

The use of the Drinker apparatus for long-continued artificial respiration forms a worth while addition to present methods of management in postdiphtheritic respiratory paralysis. Two case reports describe one recovery and one death. The early use of the method should conduce to fewer deaths from this uncommon but serious complication of diphtheria.

REFERENCES

- 1 Wilson James L.: New England J Med. 205 597 1931; *ibid* 206 887 1932
- 2 Drinker P., and McKhann O F J A. M. A. 92 1658, 1929
3. Drinker P., Shaugnessy T J., and Murphy D P J A M A. 95 1249 1930
Drinker, P and Shaw L A J Olla. Invest 7 220, 1929 and 8 38, 1930
Drinker P Lancet 1 1186 1931
- 4 Jackson D E J Med 11 515 1930
- 5 Murphy D P., and Coyne R. A J A. M. A. 95 385, 1930
Murphy D P, Bowman J E., and Wilson R. B: Am J Dis Child. 42 10, 5
1931.
Murphy D P, Wilson R B., and Bowman, J E.: Am J Obst. & Gynec 21
528 1931.
6. Wightman, H B. and Shaugnessy T J J A. M A. 93 450, 1929
Murphy D P Drinker C K. and Drinker, P Arch. Int. Med. 47 424 1931
- 7 Shaw E B., Tholander, H E., and Linper, M A. California and West. Med.
35 5, 1921
Favill J., and Fentress, T L J A. M A 97 1464 1931.
Shambaugh, J E., Jr Harrington, W G., Jr., and Ferrell, J L. J A M. A.
94 1371 1930

spinal roots and the cauda equina Plexiforme neuromas are quite similar to the multiple neuromas, the main difference lying in the fact that only a small group of nerves is affected, the lesions being more circumscribed At times, the involvement may be so great that considerable enlargement of the extremities occurs, the condition then being known as elephantiasis neuromatosa (pachydermatocele) Pigmented nevi are commonly present as associated lesions of the skin, and occasionally "port-wine" nevi and the so-called anemic nevi of Vorner¹ It should be stated that according to Antoni,² the tumors of von Recklinghausen's neurofibromatosis are made up characteristically either of apolar tissue (type B) showing no palisading of nuclei or polarization of cells, or, at times, of tissue of the A type, the true perineural fibroblastomas which are of neoplastic nature and composed of fibroblasts displaying both palisading of nuclei and polarization of cells

In cases of neurofibromatosis, the pigmented eruption of the body, or "café au lait" spots, has always attracted attention It is usually found scattered irregularly over the body Its relation to the problem of the origin and formation of skin pigmentation is of particular interest Block⁸ believes that there are two types of skin pigment cells, the melanoblasts, comprising those cells which are capable of forming pigment, and the melanophores or chromatophores, consisting of those cells which cannot elaborate their own pigment but which obtain it from other sources The human skin contains pigment in its ectodermal and mesodermal parts The ectodermal pigment cells of the skin, as well as of the mucous membranes, are melanoblasts of ectodermal origin and are found in the epidermis, especially in the basal cells, the hair matrix and in the cells of pigmented nevi The mesodermal part of the skin, the corium, contains two different kinds of pigment cells The one type, melanophores, which have phagocytized pigment, is found in the papillae and in the deeper layers, whereas the other type, mesodermal melanoblasts which have elaborated their own pigment, is found in the cutis Moehlig⁹ states that both the posterior portion of the pituitary gland and the suprarenal cortex are concerned with pigment formation, the latter reflecting or mirroring the state of the former Posterior pituitary lobe extract is a melanophore stimulant and affects particularly mesodermal tissue The pigmentary changes occurring in von Recklinghausen's neurofibromatosis have been attributed to a disordered state of the adrenal glands Many cases have been reported in the literature, such as those by Levin¹⁰ and by Tucker,¹¹ which seem to show a relationship between certain endocrine dysfunctions and neurofibromatosis The latter author states that from the pituitary standpoint the characteristics are chiefly acromegalic in type, whereas the suprarenal manifestations are pigmentary disturbances, lowered blood pressure, and hypotrichosis

The true character of the osseous lesions in neurofibromatosis was first described by Brooks and Lehman¹² who found the following types of bone changes which were considered characteristic of the disease: scoliosis, abnormalities of growth, irregularity of the shafts of the long bones, and subperiosteal bone cysts. The irregularity of the shafts of the long bones varied from slight change in outline of the periosteal and cortical structures to large tumors projecting from the surface of the bone or embedded as cyst like cavities in the structure of the bone. Microscopically, the central portion of the tumor was found to consist of tissue similar to that of the cutaneous lesions, as well as of some newly forming bone. The investigators were of the opinion that the changes were induced by the development of neurofibromas along the nerve filaments in the periosteum, thereby setting up a certain amount of reaction and causing bone destruction and regeneration. Lehman¹² has attempted to classify the various osseous lesions, defining them as manifestations of the complicated disorder of neurofibromatosis and comparing them to its skin and visceral expressions. Recently, Weber,¹⁴ in an article dealing with periosteal neurofibromatosis, also expressed the opinion that in certain cases of von Recklinghausen's disease bony thickenings occur which are due to involvement of the periosteum.

It should be borne in mind, however, that von Recklinghausen's neurofibromatosis is not seen always in its complete clinical form. As Goodhart¹⁵ has stated: "Aside from typical forms of neurofibromatosis, there are also incomplete or abortive forms in which only one of the cardinal symptoms is present, either pigmentation or fibroma which may be not infrequently combined with mental defects or skeletal anomalies." Many years ago, Weber¹⁶ called attention to the fact that cases occur in which pigmentation of the skin is manifest long before the appearance of neurofibromas of the nerve trunks or tumors of the skin, citing many case records to bear out his contention.

The following case reports illustrate the above statements.

CASE 1.—J. E. male white was born at full term on October 8, 1922. The second stage of labor was prolonged and was terminated by the application of forceps. Marked ecchymoses and swelling were present about the infant's eyes. Respiration was spontaneous; there were no convulsions. The birth weight was 10½ pounds (4.76 kg.). The mother, a primipara, was thirty-one years of age and had been married eleven years before giving birth to this boy, her only child. Throughout pregnancy she had maintained good health. There were no previous miscarriages. The father, thirty-eight years of age, was normal physically. The family history was essentially negative.

The infant was fed artificially and manifested an excellent rate of growth, weighing 25 pounds (11.4 kg.) at the end of the first year of life. Development was also normal. Of importance in the light of future developments, is the fact that shortly after the birth of the infant, the mother noticed a few scattered areas of brownish pigmentation on his body. However, little attention was paid to the eruption at this time. It should be stated here that the pigmentation became more evident sub-

sequently, new areas appearing on the trunk, face, and extremities, each lesion growing in size and deepening in hue. Aside from an attack of whooping cough when he was three years of age, and a retropharyngeal abscess at three and one-half years of age, the boy enjoyed apparent good health up to about five and one-half years.

At this time, he was seized suddenly at night by an attack of projectile vomiting which was followed shortly by a series of convulsions lasting about twelve hours. The temperature was high. He was taken to one of the city hospitals where he was observed for a period of three weeks, no definite diagnosis being made. Following this primary acute attack, the boy became subject to the frequent occurrence of convulsions, both minor and major in severity, some being of but brief duration whereas others lasted from ten to fifteen minutes. For the most part they took place at night while the boy was asleep. They were preceded invariably by sharp piercing cries, pallor and cyanosis and were followed by clonic contractions of the entire body and a period of unconsciousness. At no time was there frothing at the mouth, biting of the tongue, or loss of sphincteric control. Vomiting did not occur always. Other episodes consisted merely of a trembling of the entire body and momentary loss of consciousness. The attacks occurred irregularly, sometimes taking place daily, whereas at other times an interval of a few weeks elapsed between attacks.

At six and one-half years of age, the boy entered public school, where it was noticed that he had poor eyesight. He was placed, therefore, in the sight conservation class. He was then referred to the Neurologic Institute for examination. It was noted by roentgenograms that the skull showed a tendency toward early union of the sagittal suture but that this had not yet produced demonstrable change in the outline of the skull. The sella turcica appeared to be normal and secondary dentition was progressing favorably. The blood gave a negative reaction both to the Wassermann and Kahn precipitation tests. The von Pirquet test was negative and the basal metabolism was recorded as being minus 3. Of interest is the fact that psychometric tests were performed at this time, with an intelligence quotient of 102 on the Terman scale.

As far as the general behavior of the boy was concerned, he was well-mannered and obedient, amenable to discipline, and never assaultive. His personal habits were good. In school, he associated well with his classmates and showed slow but definite progress in class work, despite frequent periods of absence. Meanwhile, it was noticed by the mother that the pigmented areas on the face and body of the boy, were increasing in number and in size and were becoming deeper tan in color. It was also observed that he was developing a hard tumor on the right side of the nose, directly beneath the inner portion of the right eye. The boy was then referred for admission to the Beth Israel Hospital.

He was now eight years of age, weighed 70 pounds (31.8 kg) and was 55 inches (139.7 cm.) in height. His head measured $21\frac{3}{4}$ inches (55 cm) in circumference, his chest $26\frac{1}{2}$ inches (65.5 cm), and his abdomen $25\frac{1}{2}$ inches (64.5 cm). He was fairly well developed and of fair nutrition. The musculature was flabby and the posture poor. He was restless and inattentive. He appeared to be dazed and disoriented, his responses showed a markedly delayed reaction time. Over the entire trunk, face, and extremities, but mainly over the covered parts of the skin, there was seen a generalized, haphazardly arranged, irregularly oval-shaped, pigmented macular eruption, the lesions varying in size from that of a pinhead to 4 or 5 centimeters in longest diameter (Fig 1). Their color ranged from pale tan to light brown. They were equally numerous both on the dorsal and ventral aspects of the trunk and extremities. Directly above and to the outer side of the right nipple there was seen a deeply pigmented nevus. The skin, which was moist and coarse, had a peculiar pale yellowish line. There was a normal growth of lanugo hair. At this time, no tumor masses were palpable in or beneath the skin.

The head was long and narrow and appeared to be too large for the rest of the body. The upper and lower jaws were prominent and the upper middle incisor teeth protruded forward markedly. The general features were gross and coarse and suggested a disturbance of the pituitary gland. It should be noted in this connection, that the fingers of the hands were long, broad and spatulate at the tips. The scalp was covered by coarse straight medium brown hair, the eyebrows and eyelashes were normal. The nose was broad both at the base and at the bridge. To the right side there was a bony hard swelling apparently intimately connected with the nasal bone. The overlying skin was freely movable. The palpebral fissures were equal, there was about a 25 degree convergent strabismus of the left eye.



Fig 1—Showing the irregularly scattered oval-shaped, pigmented eruption of the body. Note also the bony tumor on the right side of the nose and the internal strabismus of the left eye.

The right pupil was greater than the left, both reacted normally to light and accommodation. The acuity of vision was 20/100 for the right eye and 20/200 for the left, there was a bilateral myopic astigmatism. The fundi showed a primary optic atrophy. Attempts to estimate the fields of vision either by confrontation or by perimetry were unsuccessful. The ears were normal. The lips were thickened, the vermillion borders being fairly well defined. The upper incisor teeth were larger than normal and protruded forward markedly. The enamel of the permanent teeth was fair. The deciduous teeth showed well advanced caries. All the teeth were poorly spaced, the occlusion was bad. The mucous membranes of the mouth were of good color. The tongue, throat, and pharynx were normal. There was no lymphadenopathy.

The thorax was symmetrical and the nipples were normal. The lungs and heart were normal. The abdomen was soft, no organs or masses were palpable. The genitals were normal in appearance and the testicles fully descended. With the exception of the broad, flat hands, as has been mentioned before, the extremities were normal, as were the nails of the fingers and toes. Both the superficial and deep reflexes were equal and active, no pathologic reflexes were elicited. The skin was hyperesthetic over all areas.

Laboratory procedures showed that the urine and the blood were normal. The latter gave a negative reaction to the Wassermann test. Glucose tolerance tests were performed, but gave no conclusive information. The spinal fluid showed negative reactions to both the Wassermann and colloidal gold tests. A basal metabolism was attempted under conditions not truly basal and showed a rate of plus 18.



Fig. 2—Atrophy of the bones of the hands involving the epiphyses and diaphyses but being more marked at the epiphyseal ends. Note beginning cyst formation in head of first metacarpal bone of left hand.

Roentgenography of the skull revealed that the cranial cavity was somewhat large, particularly in the postauricular portion. The bones of the cranium were of normal thickness, there were no areas of bone destruction or sclerosis and the sutures were not separated. The sella turcica was normal and the air sinuses were well developed. In the right infraorbital region, in the neighborhood of the superior maxilla, there was seen a bony mass which showed normal bone markings and which appeared to be a part of the ethmoidal cells. This mass was evidently that seen externally to the right side of the boy's nose. Encephalography failed to show any definite pathologic condition of the brain. Roentgenograms of the bones of the hands revealed atrophic changes involving the carpal and metacarpal bones, as well as those of the phalanges (Fig. 2). The atrophy was very distinctive and involved the epiphyses and the diaphyses, but was most marked at the epiphyseal ends. In the head of the first metacarpal bone of the left hand, there was seen coalescence of several lamellae.

which showed changes resembling beginning cyst formation. Similar changes were found to be present in the bones of the metatarsal phalanges, as well as in the bones of the shoulder and hip joints. Films of the chest revealed nothing unusual.

After a prolonged period of observation in the hospital, during which time the boy had but one mild attack of convulsions, he was discharged. Since then for the past year, the convulsive seizures have occurred frequently, being both of minor and major severity. Whereas previously they took place about once a week, of late they have happened almost daily. Throughout all this time, his general behavior has been fair. However, he has been showing signs of progressive mental and physical deterioration. Mentally, he is unable to grasp new situations easily, his reaction time has increased considerably, and he appears dazed and inattentive. He is unable to concentrate on even the simplest problem and his answers to questions are irrelevant. He seems also to have reached the limit of his learning capacity.

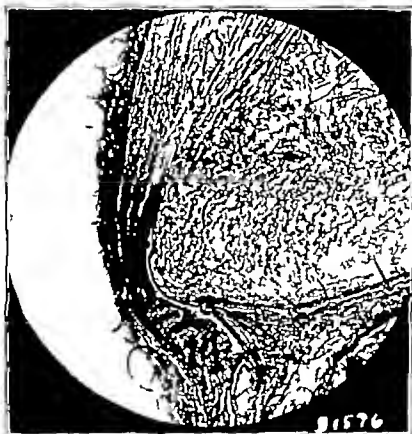


Fig 2—Photomicrograph of section of subcutaneous nodule showing nerve trunk and tumor

Physically he has shown a slow but steady loss in weight. Transient pathologic reflexes appear from time to time. He walks shakily swaying from side to side and shows a general lack of motor coordination.

At a recent follow up examination it was noted that several small subcutaneous nodules had developed bilaterally along the course of the superficial branches of the ulnar nerves. In addition a few had appeared in the occipital areas of the scalp. The boy was then readmitted to the hospital and a biopsy was performed, two of the subcutaneous tumor masses being removed. Grossly the specimens consisted of spindle-shaped swellings having smooth shiny gray surfaces and were firm and elastic in texture. The microscopic report confirmed the clinical diagnosis of von Recklinghausen's neurofibromatosis. The spindle-shaped swellings consist of a highly edematous network of fibers. The fibers are coarser in the center thinner at the periphery. The edema is very marked at the periphery. The fibers are continuous with fibers from the nerve which are stretched over the node. How far these fibers belong to the nerve proper how far to the endoneurium cannot be said with cer-

tainty The same doubtful behavior is evidenced in the van Gieson stain, where the thicker fibers become intensely red, while the thinner ones, which are continuous with them, are definitely yellow There is a very fine network of yellow fibers through which nuclei are spread in irregular fashion Most of the nuclei are ovoid or spindle shaped Occasionally, larger, faintly staining plasmatic bodies are seen around the nucleus In the nonthickened portions of the nerve at the end of the specimen, the endoneurium appears much thickened On the cross section, however, the medullary sheath and axis cylinders appear normal, as far as can be judged in this preparation" (Fig 3)

Comment—In recapitulation, Case 1 is one of neurofibromatosis in a young boy, nine years of age, showing clearly the systemic nature of the disorder The boy presented pigmented lesions of the skin, subcutaneous peripheral nodules, and definite bony changes In addition, there were signs of involvement of the central nervous system, as was manifested by epilepsy, signs of progressive mental deterioration, and changes in the optic nerve discs, as well as by acromegaly features Of interest is the fact that the "café au lait" spots were noted shortly after the birth of the child The onset of convulsions came about five years later Bony changes were noted when the boy was about eight years of age whereas the peripheral neuromas appeared only recently

CASE 2—D W a white girl, four years of age, was admitted to the Beth Israel Hospital on December 15, 1931, because of a marked swelling of four days' duration on the back of the left shoulder The complete history, however, antedated considerably this present period of illness, for, during the previous year and up to about four weeks prior to admission to the hospital, the child had been subject to the irregular appearance of small tumors over the scalp and forehead They were neither painful nor tender, lasted a short time, and disappeared of their own accord They caused no impairment of the child's physical development or any change in her general behavior At no time was there fever or other constitutional symptoms An interval of about one month lapsed following the subsidence of the last swelling, when the mother noticed the presence of a new, rapidly growing mass over the posterior aspect of the girl's left shoulder The swelling was much larger than any of those which had occurred previously, but again, there were no general symptoms, whereas locally there resulted only slight limitation of motion of the left arm and some stiffness of the neck

As far as the child's developmental history is concerned, it was apparently normal in all respects She was born at full term and weighed $5\frac{1}{4}$ pounds (2.38 kg) at birth The delivery was normal, respirations were spontaneous, and there were no convulsions The child was breast fed for a period of five months and then was given cow's milk and the usual mixed diet The trend of motor development proceeded normally At four months, the child was able to support its head She sat up erect at five months, crept at seven months, stood up supported at eight months, walked freely at fourteen months, and spoke single words at twelve months of age The first tooth erupted at about six months Aside from a bilateral suppurative cervical adenitis at two years of age, the child had always enjoyed good health

The family history was essentially negative The mother, thirty one years of age, the father, forty years of age, and their only other child, a boy of twelve years, were all normal physically There was no history of familial or hereditary diseases either in the maternal or paternal branches of the family

Physical examination showed a quiet, mild mannered, obedient little girl who was in no apparent pain or distress. The body temperature was 99.4 F., the pulse rate was 110, and respirations 28 per minute. She was well nourished and had good musculature and color. Her weight was 39½ (17.7 kg) and her height 40 inches (101.6 cm.) The circumference of the head was 18¾ inches (47.6 cm) and that of the chest 22¾ inches (57.8 cm). Her neck and head were held in a protective posture and there was some limitation of motion of the former to the left. The left arm was favored and could neither be raised above the level of the shoulder nor rotated without resistance on the child's part. The pectoral and scapular groups of muscles on the left side seemed peculiarly spastic to palpation. Over the left shoulder was seen a large diffuse swelling which extended anteriorly outward and forward from the base of the neck to the supraclavicular area, and posteriorly backward and downward to a point below the tip of the scapula. Laterally it ex-



FIG. 4.—A. Photograph taken on admission to hospital, showing the diffuse swelling of the left side of the back and of the left side of the neck. B. Showing the marked swelling of the left pectoral region occurring three months later.

tended from the spinal column to the posterior axillary line. (Fig. 4 A and B) The mass was warm, firm, brawny, and slightly tender. Its edges were poorly defined and merged with the adjacent tissues. It was intimately attached to the underlying structures and to the overlying integument which was reddened, tense, and somewhat glossy. The superficial veins showed prominently. Comparative skin temperature determinations revealed little thermal difference between the swollen area and a symmetrical area on the opposite side. Directly below the large mass, a smaller, but similar swelling was also present. There was some brawny edema of the supra-pubic region. Elsewhere the skin was smooth, moist, and showed the usual growth of lanugo hair. There was no regional or general lymphadenopathy.

The head was symmetrical and the scalp, as well as the eyebrows and eyelashes, showed a good growth of soft, smooth, medium brown hair. The palpebral fissures

and the pupils were equal, the latter reacting promptly to light and accommodation. The eyegrounds were normal. The nose, mouth, throat, and ears showed nothing abnormal. All of the deciduous teeth had erupted, they were well formed, had good enamel, and showed no evidence of caries. As has been stated, the neck showed marked fullness on the left side. The trachea was in the midline, there were no abnormal pulsations. The heart, lungs, and abdomen were normal. The liver and spleen were not enlarged. The extremities were normal with the exception of limitation of motion of the left arm. The nails of the fingers and toes showed nothing unusual. Superficial and deep reflexes were equal and active, there were no abnormal reflexes.

The urine, blood counts, differential smears, and chemistry of the blood were normal. The Wassermann reaction of the blood and the von Pirquet test were negative. Roentgenograms of the chest, cervical and thoracic vertebrae, and of the left shoulder girdle revealed nothing of importance. Films of the skull showed changes suggesting an internal hydrocephalus. Bearing in mind the possibility that the swellings might have been allergic in origin, various protein sensitivity tests were done, but they gave no definite information.

During the early part of the child's stay in the hospital, the mass on the left side of the back, fluctuated in size, sometimes appearing smaller and being softer to touch, whereas at other times it was considerably larger and firmer. The limitation of motion of the left arm became more marked, as did the spasticity of the underlying groups of muscles. It was thought that microscopic examination of the tissue which formed the mass, would be of value in the diagnosis of the case. Accordingly a biopsy was done, the smaller swelling being excised under local anesthesia. The gross pathologic examination showed a piece of skin having a thick, glassy subcutaneous layer which measured about 1.4 centimeters in depth. Microscopically, the upper layers of the skin were normal, there was no trace of edema. The cutis was normal, as were the upper layers of subcutaneous fat. In the deeper tissues, however, there was seen a fibroma containing some nerve fibers at its periphery (Fig. 5). According to the report of the pathologist: "The tumor obviously belongs more to the fibromatous type of Recklinghausen's disease. Nerves are seen at its periphery. They are well separated from the surrounding tumor tissue. At low magnification, the interlacing of fibers immediately evokes the idea of neurofibroma. Throughout the tumor, thick, obviously fibrous bands are seen stained intensely with the acid fuchsin. The remainder of the tumor consists of a fine reticulum which assumes an orange hue in the van Gieson stain. At many points it has a similarity with nervous tissue, but there is no definite proof. The many elongated, fairly light staining nuclei show fibrillary prolongations at many points. Whether or not the reticulum has been formed by these cells cannot be stated. There are some groups of larger cells which are not characteristic of any definite histologic structure. No palisade arrangement of nuclei is seen. The tumor is situated way below the cutis, therefore nothing can be said about its relation to the sweat glands. Diagnosis: Neurofibromatous type of von Recklinghausen's disease."

After a period of observation, the child was discharged from the hospital. The swelling had subsided considerably, but the area remained indurated. The subsequent clinical course is of interest, in so far as new tumor masses appeared from time to time in different regions of the child's body. These swellings grew slowly, were similar in appearance and, after reaching their height of development, subsided gradually but never disappeared entirely. About one month following her discharge, the girl was seen in the follow-up clinic. Some swelling was still present on the left side of the back. There also seemed to be beginning involvement of the entire left pectoral area. The subcutaneous tissue was brawny to palpation. The left arm could not be raised voluntarily above the level of the shoulder, the underlying muscles were spastic. The right side of the back also showed evidence of in-

volvement, for just to the right of the spinal column, at the level of the lower thoracic vertebrae, a tumor measuring about 4 by 6 centimeters was visible. At the next examination, a month later a new swelling was seen on the posterior aspect of the right side of the neck causing considerable limitation of motion of the head. Shortly after a large mass developed over the left pectoral region. This swelling was again firm, warm, somewhat tender, and indefinitely demarcated from the surrounding tissues. At her last visit to the clinic, the child showed a recurrence of the swelling at the base of the left side of the neck. It was then learned that the child had entered another hospital for a period of observation. Information from that source showed that the disorder was also diagnosed as that of neurofibromatosis. Of interest is the fact that at this time roentgenograms of the various bones revealed many exostoses, some of which were associated with the tumor masses. Roentgen therapy was given the tumors diminishing in size.

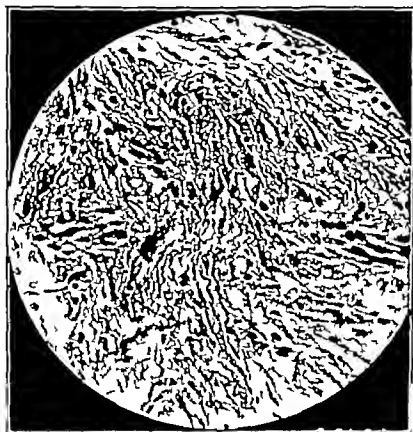


Fig. 5.—Photomicrograph of section of biopsy specimen. Note the thick interlacing fibrous bands and the fine reticular network.

Comment—Case 2 is one of neurofibromatosis in a girl of four years, and is presented because of the unusual character and distribution of the cutaneous lesions and because of the lack of constitutional symptoms. The history was that of the development of large indurated masses in the cervical, pectoral, scapular, lumbar, and pelvic regions of the body. These swellings were subject to marked fluctuations in size. Biopsy revealed the characteristic pathologic changes of neurofibromatosis. Subsequent roentgenographic examinations showed beginning osseous changes.

BOURNEVILLE'S TUBEROUS SCLEROSIS

Closely related to von Recklinghausen's neurofibromatosis, is the disorder which is known as tuberous sclerosis, a fairly rare congenital

malformation of ectodermal derivation, also affecting the brain, skin, and other organs of the body, and being associated invariably with epilepsy and feeble-mindedness. It is sometimes known as "epiloia," a name proposed by Sherlock¹⁷ in 1911. This term has been objected to by Babonneix¹⁸ on the grounds that Sherlock merely redescribed and renamed the clinical picture of Bourneville's tuberous sclerosis.

Tuberous sclerosis was first described by Bourneville¹⁹ in 1880. He reported the pathologic changes occurring in the brain of a three-year-old epileptic girl who presented clinically signs of arrested physical development, hemiplegia, idiocy, and "acne rosacea and pustulosis of the face." At necropsy islets of hypertrophic sclerosis were found distributed over the cerebral hemispheres. The brain showed also an anomaly of the olivary bodies. Shortly after, Bourneville,²⁰ in collaboration with Brissaud, described another case in a four-year-old boy who suffered from convulsions. Autopsy revealed similar sclerotic lesions of the cerebral convolutions, in addition to a large hemorrhage in the right frontal lobe, arterial anomalies, and a congenitally malformed heart. However, it remained for Bundschuh²¹ and for Bielschowsky and Gallus²² to describe independently the minute histologic alterations occurring in the tumors of the brain in tuberous sclerosis.

Of interest are the cutaneous manifestations of tuberous sclerosis, the warty nodules occurring on the face and known as "adenoma sebaceum" or "nevus multiplex of Pringle." In 1890, Pringle²³ reported in a number of patients the presence of "indolent, firm, whitish, or yellowish, sago-grain-like, solid papules or little tumors, unbedded in the skin at different depths, or projecting from it. Intimately intermingled with these lesions and transgressing their limits in every direction, especially over the cheeks towards the ears, are innumerable capillary dilatations and stellate telangiectases." He recognized two elements in the face lesions, the one, a familiar, transitory form of "rosacea," and the other, an unfamiliar, permanent, neoplastic condition of the sebaceous glands, nevroid in character. He also noted that the eruption appeared to occur in subjects generally mentally below par. Pringle grouped these cases under the name of "adenoma sebaceum," but he gave due recognition to the fact that in 1885 Balzer²⁴ proposed the name in reporting a similar type of eruption of the face. He also made mention of an unpublished note by Hollopeau on a case of "sebaceous, miliary telangiectatic adenomata." Jadassohn²⁵ was the first, however, to appreciate the true significance of this anomalous condition of the skin and showed that it was neither an adenomatous nor a hyperplastic condition of the sebaceous glands. Rather, the lesions belong to the nevroid group of disorders and consist mainly of

hyperplastic connective and vascular tissues. They are part of the widely distributed disorder of tuberous sclerosis.

That tuberous sclerosis is a widespread systemic disorder, as was adduced by Kufs²⁰ in 1913 is evidenced by the fact that at autopsy gross abnormalities, such as cysts and tumors are found in other internal organs. The kidneys and the heart are most frequently affected although involvement of the pancreas, liver and other organs may also occur. As has been reported by Koenen,²¹ the disease may show hereditary and familial tendencies. It may be present at birth or become manifest in early or even in late childhood. According to Yakovlev and Guthrie¹ it is the most typical and clearly defined of the neurocutaneous syndromes in both its clinical and pathologic manifestations.

ENCEPHALOTRIGEMINAL ANGIOMATOSIS

It is a moot question whether the clinical picture of angiomas of the brain with vascular nevi of trigeminal distribution should be included in the so-called group of neurocutaneous syndromes. As Yakovlev and Guthrie¹ have stated: 'Indeed the pathology of the vascular neurocutaneous syndrome at first sight obviously consists of congenital malformation of the blood vessels—a tissue, not of ectodermal but of mesodermal derivation.' The authors present evidence however in favor of the neurogenic (ectodermal) origin of this vascular anomaly. They are of the opinion that "the blood vessels of the nervous system, of the skin, of the retina and also certain of the glandular organs are the tissues of election for angiomas as compared, for example, to tissues of nonectodermal origin, such as bone and muscle.' The distribution of the nevi corresponds, furthermore, apparently with zones of sympathetic innervation suggesting that the vascular defect may have its origin in some maldevelopment of vasomotor origin. This fact receives added weight from the studies on the capillary circulation of the skin by Jaensch²² who believes that the development of cutaneous capillaries is dependent in great degree upon the time of melanization of the nerves and the differentiation of the cerebral cortex. The work of Weber²³ has shown also that the telangiectatic 'port wine' nevi are apparently neurogenic in nature. It should be emphasized that the mesodermal hyperplasia may be present in varying degrees in all three congenital disorders either as an accompanying condition or overshadowing entirely the ectodermal malformation.

In their monograph on tumors arising from blood vessels of the brain Cushing and Bailey²⁴ state that these vascular newgrowths may be divided into two major groups, the angiomatous malformations and the angiomatous or true neoplasms of blood vessel elements. The angiomatous malformations are due to some defect of develop-

ment and contain traces of compressed nerve between their vascular loops, thereby differentiating them from the blood vessel tumors proper, the angioblastomas, which are composed solely of mesodermal tissue. Angiomatous malformations may be predominantly capillary (telangiectatic), venous (angioma venosum), or arteriovenous (angioma arterialis) in their structure. Capillary malformations may occur in various parts of the brain, such as deep in the brain stem, and seldom give rise to symptoms, whereas the venous and arteriovenous angiomas are primarily surface lesions of the cerebral hemispheres, occasionally the hindbrain, and are often provocative of epileptiform seizures. At times the angiomatous newgrowth extends with its apex toward the ventricle.

The venous angiomas are of interest in that they may be associated with nevi in the region of the distribution of the trigeminal nerve, a fact of importance in the early recognition of this form of vascular lesion, as compared with arterial angiomas whose presence are difficult of detection unless they are accompanied by an audible bruit or the secondary effects of aneurysmal communications giving rise to enlargement of extracranial vessels. At times, venous angiomas are associated with aneurysmal lesions and occasionally with unilateral exophthalmos. In recent years, Weber,³¹ Dimitri,³² Marque,³³ as well as others, have described cases in which congenital trigeminal nevi were found to be associated with calcified homolateral angiomas of the brain, usually in the occipital area. The majority of the cases occurred in young children in whom epilepsy, mental defect, and unilateral buphthalmus (or glaucoma) were outstanding features.

As has been previously stated, the angioblastomas are true vascular neoplasms and are to be clearly differentiated from the angiomatous malformations. According to Cushing and Bailey,³⁰ angioblastomas are rarely, if ever, accompanied by nevi. They are usually found in the cerebellum, occasionally in the medulla oblongata or in the cord, and they may be either cystic or solid in structure. They were first described in 1926 by Lindau³⁴ who recognized their true nature while making a study of cysts of the cerebellum. Microscopically, the angioblastomas show a sharp demarcation between the tumor proper and the surrounding nerve tissue and exhibit a marked tendency toward cyst formation. Lindau found also that the angioblastomas are frequently accompanied by concomitant malformations or tumors of somatic organs, such as cysts of the kidneys and pancreas. In addition there may occur vascular newgrowths of the retina.

The angiomas of the retina alone have long been known by ophthalmologists under the name of von Hippel's disease.³⁵ However, they were really first recognized in 1894 by Treacher Collins³⁶ who described two cases, in brother and sister, presenting peculiar vascular newgrowths affecting the retinal structure of both eyes. Collins

wrote that "It was made up of a plexus of numerous very thin walled blood vessels and there are in it cystic spaces. It may therefore, best be described as a capillary nevus, which in places has undergone cystic degeneration." According to Lindau²⁷ 25 per cent of the cases of von Hippel's disease give rise to symptoms of brain complications and 20 per cent of the cases have been found to be familial. Möller²⁸ has called attention to the familial nature of the disease and Rochat²⁹ has published his experiences with one family in which the factor of heredity was demonstrable for three generations.

In a recent symposium on the problem of vascular newgrowths of the brain, Lindau²⁷ stated that

I have adduced good evidence that the subdivisions of the vascular newgrowths into two major groups, angiomatous malformations and hemangioblastomas have been well established and means a great improvement, both clinically and pathologically. Further I have shown that each of these groups includes a general systemic disorder: the first a cavernous angiomatosis of the brain and skin, associated with buphthalmus, but no underlying angioma causing eye lesion, and the second, a capillary angiomatosis of the cerebellum and the retina with coordinated lesions of the abdominal organs. Thus both these systemic disorders, although related and rather alike, clearly differ and as we have never met with a coincidental occurrence of these two conditions in the same family it would be better at the present stage not to mix them up.

Case 3 is presented as an example of the clinical picture of calcified cavernous or venous angioma of the brain associated with nevi in the region of distribution of the trigeminal nerve. The pathologic features of this case have been considered elsewhere by Brock and Dyke.⁴⁰

CASE 3.—S. L., a white boy was born at full term on May 12, 1925. The delivery was normal, there were no convulsions. The mother a multipara, was thirty-four years of age, physically normal, and throughout pregnancy had suffered no illnesses. Her first two pregnancies terminated in miscarriages at three months. Subsequently she was delivered of four normal children. The father was thirty-nine years of age, and, at about this time was treated surgically for a gastric ulcer. The family history was essentially negative.

At birth the infant weighed 7 pounds (3.18 kg). He was nursed for about sixteen months, and in addition, from six months on, received cereals, fresh vegetables, and orange juice daily, but no cod liver oil. At about four months, the infant was able to hold up his head. He sat up erect at six months, and stood up supported at about eight months, but did not pass through either the crawling or creeping stages of motor development. Walking was delayed markedly until about four years of age. The reason for this retardation will be explained subsequently. The first tooth erupted at five months. Babbling began at six months of age but the development of speech never progressed beyond this rudimentary stage. Early perceptual and social development followed apparently a normal trend. At approximately six months of age the child showed signs of recognizing and smiling at the various members of the family. He was also able to distinguish between strangers and friends.

The first period of illness occurred when the infant was nine months of age. He was then admitted to the Beth Israel Hospital with a history of three days' duration, characterized by convulsions and weakness of the right upper and lower

extremities On admission, the temperature was 105° F There was drowsiness, nystagmus of both eyes, and clonic contractions of the right side of the body A nevus was also noticed on the right side of the forehead, but its full significance was not realized at this time The left ear showed a purulent otitis media The fundi of both eyes appeared to be normal, but it was noted by the ophthalmologist that the infant did not react promptly to the influence of light A spinal puncture was attempted, but a bloody fluid was obtained The Wassermann reaction of the blood was negative With the subsidence of the acute symptoms, the infant showed a complete paralysis of the right upper and lower extremities After a period of convalescence, he was discharged from the hospital his condition having been diagnosed as that of polioencephalitis

For the next two years the child was observed in the follow up clinic During this time, he was subject to attacks of convulsions which occurred at irregular intervals and which were accompanied by brief periods of unconsciousness Occasionally the child had several convulsive seizures a day, whereas at other times



Fig 6 — Port-wine nevus of the right side of the forehead and face in the regions of distribution of the first and second branches of the trigeminal nerve.

many weeks intervened between attacks He was irritable, restless, and slept poorly He lacked urinary control and soiled himself frequently General motor and manipulatory control was greatly retarded The weakness of the right upper and lower extremities showed only slight improvement Apparently, he understood gestures and spoken commands, and he was amenable to discipline It was also observed that although he reacted to stimulation from bright lights, his sense of perception was poor It is interesting to note in this connection that improvement was noted in tactile sensitivity and in the appreciation of the attributes of space Hearing appeared to be normal

At six and one-half years of age, the boy was readmitted to the hospital in order to ascertain whether the nevus of the face was associated with a similar vascular lesion of the central nervous system He now weighed 56 pounds (25.4 kg) and was 43½ inches (110.5 cm) in height The circumference of his head was 19½ inches (49.5 cm) and that of his chest 28 inches (71.1 cm) He was well nourished, had good subcutaneous fat and the mucous membranes were of good color With the exception of the paralyzed limbs, the musculature was firm His general attitude and behavior was that of the idiot In bed, he tossed from side to side, hitting

his head or face with his hands or holding his fingers in his mouth. He uttered peculiar, meaningless sounds. It was impossible to attract or to hold his attention. When erect his weight was thrown upon the right lower extremity his right foot was held everted. The right hip was flattened and there was a compensatory scoliosis of the lumbar spine to the left side. When assisted he walked by stepping forward on the left foot, then dragging the right foot up to meet it.

The skin was moist and coarse and showed a normal growth of lanugo hair. The hair of the scalp, eyebrows and eyelashes was straight, coarse and medium brown. It may be noted here that the nails of the fingers and of the toes were normal. The head appeared to be smaller than normal and was definitely flattened on the left side posteriorly. The right side of the face was larger than the left side. On the right side of the forehead there was seen a large raised port wine nevus, vivid red in hue and irregularly oblong in shape, measuring approximately 11 centimeters in length and 4 centimeters in width (Fig. 6). It began just beneath the hair line and ran obliquely downward and inward to the bridge of the nose, then spread out irregularly over the right upper eyelid. A similar but smaller nevus of irregular shape was also present on the right side of the upper lip and an additional one of oval shape and about 5 centimeters in its longest diameter on the left vertex area of the scalp.

The right palpebral fissure was narrower than the left. The pupils were regular and reacted normally to light. The eyeballs could not be examined properly. The ears were normal. The nose was flattened at the bridge, its base was broad. There was no obstruction to nasal breathing. The lips were thickened, but the vermilion borders were well defined. The incisor teeth of the upper jaw protruded prominently, the lower jaw receded markedly. Ten permanent teeth had erupted and of these, all four first molars showed advanced caries. The enamel was fair. All remaining deciduous teeth showed marked disintegration, the stumps being stained brownish black. The tongue was normal and protruded in the midline. The neck was normal. There was no lymphadenopathy.

The chest was symmetrical, both nipples were normal. The heart and lungs were normal. Neither the liver nor spleen was palpable. No abdominal masses were present. The genitals were normal in size and the testicles fully descended. Both the right upper and lower extremities showed spastic paralysis and considerable muscular atrophy. However the fingers of both hands were flexed and could be extended backwards easily. There was definite shortening of the paralyzed limbs. All deep reflexes were hyperactive on the right side. The right abdominal and cremasteric reflexes were diminished and there was a right-sided Babinski reversal, as well as a prolonged ankle clonus. The skin was hyperesthetic.

In view of the history of convulsions, progressive mental deterioration and physical signs of central nervous system involvement together with the presence of the extensive nevus on the forehead a clinical diagnosis was made of angiomatous tumor of the brain associated with a nevus of the forehead in the region of the distribution of the trigeminal nerve. Encephalography substantiated the diagnosis (Figs. 7 A B). The cranial cavity was relatively small but the bones were of normal thickness. The diploetic layer was normal. There were no evidences of increase in intracranial pressure except that the floor of the middle fossa was somewhat depressed and narrow. The sella turcica was small. There was no diastasis of the sutures or of the fontanelles. The cerebral pathways were normal in size but were slightly diminished in number. They extended well forward over the frontal area on the right side but were obliterated on the left side. There was defective outlining of the ventricles and on the left side a porencephalic cyst communicated with the ventricle. The cranial contents were shifted to the left side. The basal cisterns could not be visualized except for an area in the region of the cisterna



A



B

Fig. 7—A Encephalograms showing the linear calcific deposits in the blood vessels of the right occipital lobe, as well as the porencephalic cyst on the left side. Note the shifting of the cranial contents to the left side.

pontis. There were irregular linear calcifications extending from the region of the lambdoid suture to that of the sella turcica. These calcifications were apparently in the blood vessels of the occipital lobe of the brain.

Comment—Case 3 occurring in a boy six and one-half years of age, is illustrative of the encephalotrigeminal variety of vascular neurocutaneous syndrome. Outstanding in the history is the cerebral injury suffered by the boy at nine months of age, leading to right sided hemiplegia, subsequent mental defectiveness, and the frequent occurrence of epileptiform seizures. Clinically, the boy showed an extensive "port wine" nevus of the right side of the forehead and face. Encephalography revealed calcific deposits in the right occipital lobe of the brain, as well as a porencephalic cyst of the left side.

SUMMARY

Attention is directed to a group of three unusual congenital disorders to which surprisingly little reference has been made in the pediatric literature. The disorders are von Recklinghausen's neurofibromatosis, Bourneville's tuberous sclerosis, and angiomas of the brain associated with vascular nevi in the region of the distribution of the trigeminal nerve. All three conditions have been classified in the general category of neurocutaneous syndromes, after the suggestion of French observers. Recently, Yakovlev and Gonthier¹ have proposed that the diseases be designated by the more descriptive term of "congenital ectodermoses."

All three congenital disorders exhibit marked similarity in their clinical manifestations and in the character and distribution of their pathologic features. Furthermore they involve electively organs, such as the nervous system, skin, retina and eyeball having their common origin in the ectodermal layer of the developing blastoderm. It should be borne in mind, however, that mesodermal hyperplasia, as is evidenced by the frequent presence of vascular nevi may occur in varying degrees in all three congenital disorders either as a concomitant condition or obscuring entirely the ectodermal malformation.

Although all three syndromes show individual and characteristic manifestations they are by no means mutually exclusive. They present signs and symptoms which overlap greatly and which exhibit an impressive range of variability. Of clinical interest is the occurrence of characteristic cutaneous anomalies which are indicative of associated maldevelopments in deeper seated, embryologically related structures such as the peripheral and central nervous systems, and which affect usually the cephalic and caudal ends of the body. The cutaneous manifestations are not purely localized lesions but are the external expressions of widespread systemic maldevelopments which affect visceral as well as somatic structures. This is evidenced by the fact that at autopsy gross abnormalities such as cysts and tumors, are found

in other internal organs. Also of importance in this group of congenital disorders is the involvement of the entire nervous system and, in addition, the frequent occurrence of epilepsy and feeble-mindedness. All three neurocutaneous syndromes show, furthermore, definite familial or hereditary tendencies.

Von Recklinghausen's neurofibromatosis is a generalized disease involving primarily nervous tissue in any part of the body with secondary changes in other organs. Characteristically there may occur polypoid tumors of the skin, subcutaneous nodular tumors of the peripheral nerve trunks, lesions of the central nervous system and of the meninges, brownish pigmentation of the skin ("café au lait" spots), secondary changes in the skeletal system, and abnormalities of development of visceral structures. The disorder is not seen always in its complete form, various incomplete or abortive forms being present in which only one of the cardinal signs is manifest.

Bourneville's tuberous sclerosis is a fairly rare congenital malformation and it is probably the most typical and clearly defined of the neurocutaneous syndromes in its clinical and pathologic features. It is a widespread disorder showing islands of hypertrophic sclerosis of the cerebral hemispheres, wart nodules of the face, the so called "adenoma sebaceum," and cysts and tumors of internal organs. It is invariably associated with epilepsy and mental defect.

The last of the group of neurocutaneous syndromes, is the clinical picture of angiomas of the brain associated with vascular nevi in the region of distribution of the trigeminal nerve (encephalotrigeminal angiomas). Although, at first sight, it consists of congenital malformation of blood vessels, a tissue of mesodermal origin, evidence is in favor of the fact that it is of neurogenic (ectodermal) origin. It should be emphasized that vascular newgrowths of the brain are divisible into two major groups, the angiomatic malformations which consist of nervous and vascular tissue, and the angioblastomas or true neoplasms which are composed solely of mesodermal tissue. The latter involve primarily the cerebellum and have been known under the name of Landau's disease. They may be either solid or cystic in structure and are accompanied frequently by malformations of visceral organs and vascular newgrowths of the retina (von Hippel's disease), but no nevi of the skin. This condition should be clearly differentiated from the angiomatic malformations which are also accompanied by general systemic malformations and by vascular nevi of the skin, as well as buphthalmus (glaucoma). Often the congenital nevi of trigeminal distribution are associated with calcified homolateral angiomatic malformations of the brain, usually of the occipital area.

Three case reports have been presented, two of them as illustrations of the varied clinical manifestations of the complicated disorder of von

Recklinghausen's neurofibromatosis, and one of them as an example of angiomatous malformation of the brain in association with vascular nevi of trigeminal distribution

REFERENCES

- 1 Yakovlev, P I, and Guthrie R. H. Arch. Neurol. & Psychiat 26 1145 1931
2. von Recklinghausen, F Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen Berlin, 188_. A. Hirschwald 138 pp
- 3 Ewing, J Neoplastic Diseases, Philadelphia, 1928, W B Saunders Co pp 164 170
- 4 Penfield, W, and Loang A W Arch. Neurol. & Psychiat 23 320 1930
- 5 Prieser S. A., and Davenport, C. B. Am. J Med. Sc 155 50, 1918
- 6 Kraus W M. The Non Traumatic Diseases of the Peripheral Nerves in Nelson a Living Medicine, New York Thos. Nelson & Sons vol. 6 pp 365 366
- 7 Antoni N Ueber Rückenmarkstumoren und Neurofibrome Studien zur Pathologischen Anatomie und Embryogenese Munich 1900 J F Bergmann, p 311
8. Block, B. Am. J Med. Sc. 177 600, 1900
- 9 Mochlig R. C. Ann. Int. Med 4 1411 1931
- 10 Levin O L. Arch. Dermat. & Syph. 4 303 1901
- 11 Tucker B R Arch. Neurol. & Psychiat. 11 308 1904
- 12 Brooks, B and Lehman, E. P. Surg Gynec. & Obst 38 597 1924
- 13 Lehman, E. P. Arch. Dermat. & Syph 14 178 1900.
- 14 Weber, F P. Quart. J Med 13 151, 1930
- 15 Goodhart, P. Neurofibromatosis in Tice's Practice of Medicine Hagerstown Maryland, W F Prior Co., vol. 10, p 665
- 16 Weber F P. Brit J Dermat 21 40, 1900
- 17 Sherlock E. B. The Feeble-Minded New York 1911 The Macmillan Co., p 235
- 18 Babonneix, L. Arch. de méd. d. Enf. 31 133, 1908
- 19 Bourneville Arch. de Neurol. 1 60, 1880
- 20 Bourneville and Brissaud, E. Arch. de Neurol 1 301 1881
- 21 Bundschuh E. Beitr. z. path. Anat. u. z. allg. Path. 54 278 1912
- 22 Bielschowsky M and Gallas J f Psychol u. Neurol 20 (Supp 1) 1 1913
- 23 Pringle, J J. Brit. J Dermat 2 1 1890
- 24 Balzer F and Menetrier P. Arch. de Physiol. Normale et Pathol. 6 564 1885 Balzer, F, and Grandhomme Arch. de Physiol. Normale et Pathol. 8 93, 1886
- 25 Jadassohn J. Arch. f Dermat. u. Syph. 117 5, 7 1914 117 705 1914 117 838 1914
- 26 Kufs, H. Ztschr f d. ges. Neurol. u. Psychiat 18 291 1913
- 27 Koenen J. Nederl. tijdschr v geneesk 75 731 1931
- 28 Quoted by Marinaccio G., Bruch, A and Buttu G. Bull. l acad. de Med. Paris 103 596 1930
- 29 Weber F P: Brit J Dermat 41 2-1 1929
- 30 Cushing H and Bailey P. Tumors Arising from Blood Vessels of the Brain Baltimore 1928 C. C. Thomas p. 211
- 31 Weber F P. J Neurol. & Psychopath 3 134 1922.
- 32 Dimitri V. Rev. Assoc. méd. argent (See Neurol. y Psiquiat) 38 63 1923
- 33 Marque A M: Rev oto-neuro-Oft (Buenos Aires) 1 202 1927
- 34 Lindau, A. Acta path et microbiol Scandinav Bapp 1 p 128 1926
- 35 von Hippel E. Klinische Monatschr für Augenheilk 33 260 1895 Arch f Ophthl. 59 83 1904 Arch. f Ophthl. 79 350 1911
- 36 Collins, E. T. Tr Ophthl. Soc United Kingdom 14 141 1894
- 37 Lindau, A. Sargent P., and Collins E. T. Proc Roy Soc Med (See Neurol. & Ophthl) 24 1 1931
- 38 Möller H U. Acta Ophthl 7 244 1900
- 39 Roehat G F. Nederl. tijdschr v geneesk 75 437 1932
- 40 Brock S. and Dyke, C. G. Bull Neurol Institute New York 2 24, 1932.

DETERMINING APPROPRIATE WEIGHT FOR BODY BUILD*

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NUTRITIONAL status has long held first place as a measure of health, and rightly so, but modern ideas of judging nutrition are changing rapidly. We know that there is a proper weight range for each child which reflects his optimum development and state of health. This proper weight depends on body build or relative width of the body as well as on height and age.

Previous studies by Gray,¹ Franzen,² Miles,³ and others have shown the relationship between various body widths and weight. Gray in 1928 proved statistically that the physical traits most highly correlated with weight were first stature, then bicristal diameter, third age, then bistyloid, then biacromial diameter, and sixth bimalleolar diameter. Gray's material consisted of 810 private school boys aged four to twenty years. He concludes "that weight is best referred to stature, next best to bicristal diameter, only third best to age, while wrist diameter is not worth further consideration. Hence it may be expected that the multiple correlation of weight with stature and bicristal diameter will be better than with stature and age."

The importance of a mathematical appraisal of observed variability was suggested by Faber⁴ in 1925. We attempted this in measuring the relationship of width to weight when both were expressed in terms of percentage deviation from the mean for the age sex group.

Dublin and Gebhart⁵ showed that present standards failed to identify a large proportion of undernourished Italian children. Turner⁶ has shown that many underweight children are not malnourished and that a perfectly healthy child may be thin because he has inherited a slender skeleton. He concludes that the skeletal type of the child should be judged as a basis for interpreting the underweight data. Clark, Sydenstricker and Collins⁷ found that a fairly large percentage of well-nourished native white children were more than 10 per cent underweight according to the Baldwin-Wood tables and they suggest that deviation from average weight need not be a criterion of physical fitness and may not be a matter of ill health or malnutrition. Consideration of body build seems to reconcile these statements with the assumptions upon which the Baldwin-Wood tables are based.

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In Faber's thorough statistical study of the heights and weights of 60,000 San Francisco school children he found that for subgroups consisting of from 400 to 600 members the mode corresponded very closely with the Baldwin Wood standards. For this reason we have based our height weight table for different body builds on the Baldwin Wood table, which established average weight for average build. Then deviation from average build determines deviation from average weight.

Faber showed an increase in weight variability with age in both sexes and a marked difference between boys and girls. Our measurements show a corresponding increase in variability of diameters with age for both sexes and a marked difference in boys and girls beginning at adolescence.

The width length index of body build as described by Lucas and Pryor² makes use of stature and bieristal diameter to designate types of build and also as a basis for weight prediction. The bieristal (or bi iliac) diameter divided by the standing height multiplied by 100 gives the width length index and is a measure of the relative width of the body. They have followed the technic of Miles and Gray in using firm pressure to get as nearly as possible measurements of the widest flare of the iliac crest. For this purpose sliding anthropometric calipers are the most satisfactory, although spreading calipers may be used.* Other body measurements were done as described by Hrdlicka³ and adopted by the International anthropometric agreement.

Our width length indices parallel Gray's bieristal stature indices at all ages and for both sexes and are consistently a little smaller. The bieristal diameter appears to be 0.6 cm (0.25 in.) less in our series than in Gray's series which may be explained on a basis of superior social economic status in Gray's private school children, since the bi cristal diameters obtained by us on our own small series of 300 private school boys are practically identical with Gray's.

The bi iliac diameter can be measured more accurately than chest width or shoulder width because it is not affected by respiratory movements or changes in posture. The greater accuracy of the pelvic measurement is shown when two or more observers measure the same children consecutively. It was found at the Institute of Child Welfare for example that for two physicians the average difference in measurement of 112 adolescent children was as follows:

Bi iliac 56 girls	2.3 mm	or % error	0.99 ± 0.05
56 boys	2.6 "		1.16 ± 0.03
Biaxromial 56 girls	4 "	" "	1.49 ± 0.05
56 boys	4.1 "	" "	1.26 ± 0.05
Lateral Chest 56 girls	3.8 "	" "	1.70 ± 0.05
" " 56 boys	4.9 "	" "	2.10 ± 0.10

*The wooden sliding caliper made by the Marine Compass Company of Hanover, Mass., proved a satisfactory instrument and is far less expensive than the standard anthropometric metal caliper.

Todd¹⁰ reported that measurements on the living body need not vary more than 5 to 10 millimeters Dahlberg¹¹ reports an average difference in millimeters for various measurements as follows bicristal 1.64, biacromial 3.31, and stature 3.56 Gray reports the difference expected and the difference accepted in his work for various measurements in millimeters as follows bicristal 1.2, stature and biacromial 2.4, and chest measurements 2-10

It seems, then, that the bicristal diameter is the width measurement of choice because it is more constant than any chest measurement, is not affected by respiration, and may be more accurately determined

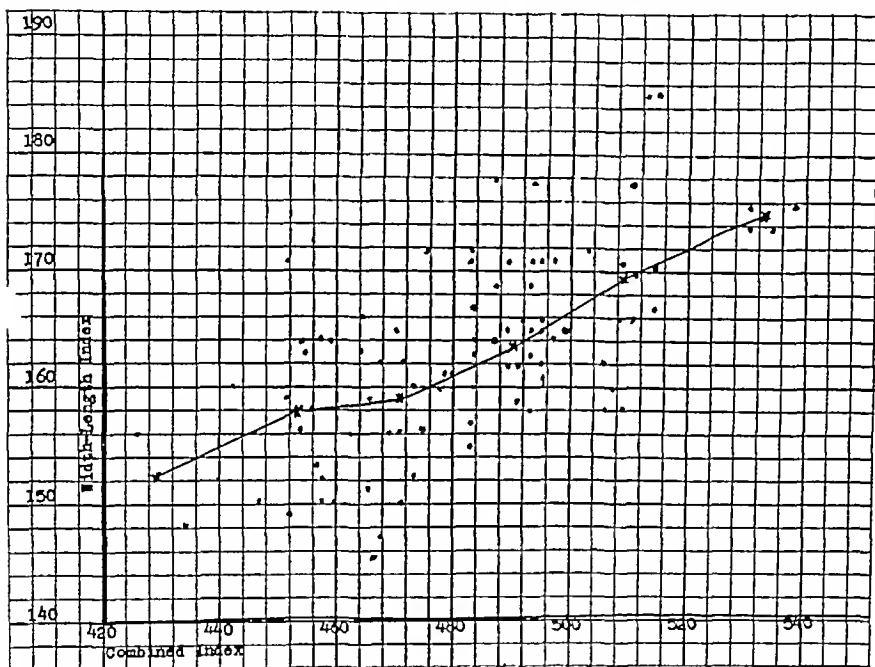


Fig 1—Width-length index plotted against combined index. One hundred and three girls ages ten eleven and twelve years

Various complicated indices of body build have been advocated, each involving several body measurements of girths and diameters. In order to see what additional information could be had from a more complicated index of build, we have plotted a combined index against the width-length index for 100 boys and 100 girls aged ten to twelve years (See Figs 1 and 2). The combined index consisted of biacromial diameter plus lateral chest diameter, plus anteroposterior chest diameter divided by stature multiplied by 100. A comparison of these chest and shoulder measurements with the single width of hips, each in percentage of standing height, shows that the single width-length index makes practically the same classification of body build as the more complicated one for the group, and is more accurately and more

easily determined. In certain individual instances where there is a lack of symmetry between pelvic and thoracic development there would be differences in the results obtained by these two methods of classification, but we think this occurs infrequently.

The relationship between relative width of the body (as measured by the width length index) and body weight was worked out first on 1000 children from Dr Lucas' private practice. It was found that the standard deviation from average weight, referred to the Baldwin Wood table, was approximately double the standard deviation from

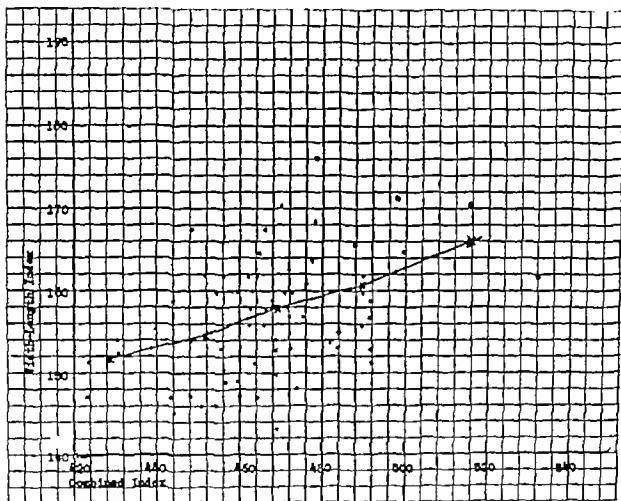


Fig. —Width-length index plotted against combined index. One hundred and three boys, ages ten, eleven, and twelve years.

the mean width length index for each age sex group when both were expressed in percentage. The study was then extended to include 2000 public school children in San Francisco, Oakland, and San Mateo, 700 clinic patients at the University of California Hospital, 300 clinic patients at Childrens Hospital, San Francisco, 300 private school boys at the Menlo School and Junior College, 200 children in the adolescent study at the Institute of Child Welfare Berkeley, and 60 children studied in a private research by Dr R. O. Moody at the University of California. Children in the endocrine clinics were excluded as were all others with serious or chronic illnesses.

Our total series of 4560 cases was divided into age sex groups for study. The same relationship between standard deviations from width and weight was found to hold for both the large series and the small series. Those width-length indices which are smaller than the mean distinguish slender-built children and the indices above the mean distinguish broad-built or stocky children. A slender-built child

TABLE I
WIDTH-WEIGHT TABLE FOR GIRLS*
SIX TO SIXTEEN YEARS

Height in Inches	Six years								Seven years							
	15 5	16 5	17 0	18 3	19 6	20 1	21 1	cm	16 2	17 2	17 7	19 0	20 3	20 9	21 8	cm
	6 1	6 5	6 7	7 2	7 7	7 9	8 3	in	6 4	6 8	7 0	7 5	8 0	8 2	8 6	in
38	26	27	28	31	34	35	36		28	30	31	34	37	38	40	
39	26	28	29	32	35	36	38		29	31	32	35	38	39	41	
40	28	30	31	34	37	38	40		31	33	34	37	40	41	43	
41	29	31	32	35	38	39	41		32	34	36	39	41	44	46	
42	31	33	34	37	40	41	43		33	35	37	40	43	45	47	
43	32	34	35	39	41	44	46		36	38	39	43	47	48	50	
44	33	35	37	40	43	45	47		37	40	41	45	49	50	53	
45	36	38	39	43	47	48	50		40	43	44	48	52	53	56	
46	37	40	41	45	49	50	53		42	44	46	50	54	56	58	
47	40	43	44	48	52	53	56		44	46	48	52	56	58	61	
48	42	44	46	50	54	56	58		45	48	50	54	58	60	63	
49	43	46	48	52	56	58	61		48	51	52	57	62	63	66	
50	45	48	50	54	58	60	63		51	54	56	61	66	68	71	
51									54	57	59	64	69	71	74	
52																
53																
Height in Inches	Eight years								Nine years							
	17 2	18 3	18 8	20 3	21 8	22 3	23 4	cm	18 1	19 1	19 6	21 1	22 6	23 1	24 1	cm
	6 8	7 2	7 4	8 0	8 6	8 8	9 2	in	7 1	7 5	7 7	8 3	8 9	9 1	9 5	in
42	31	33	34	37	40	41	43		37	39	40	44	48	49	51	
43	32	34	36	39	41	44	46		38	41	42	46	50	51	53	
44	35	37	38	42	46	47	49		40	43	44	48	52	53	56	
45	37	39	40	44	48	49	51		43	45	47	51	55	57	59	
46	38	41	42	46	50	51	53		44	47	49	53	57	59	62	
47	40	43	44	48	52	53	56		47	50	51	56	61	62	65	
48	43	45	47	51	55	57	59		49	52	54	59	64	66	69	
49	44	47	49	53	57	59	62		52	55	57	62	67	69	72	
50	47	50	51	56	61	62	65		54	58	60	65	70	72	76	
51	49	52	54	59	64	66	69		57	61	63	68	73	75	79	
52	52	55	57	62	67	69	72		59	62	65	70	75	78	81	
53	54	58	60	65	70	72	76		62	66	68	74	80	82	86	
54	57	61	63	68	73	75	79		65	69	71	77	83	85	89	
55	59	62	65	70	75	78	81		68	72	75	81	87	90	94	
56	61	65	67	73	79	81	85									
57																
58																
Height in Inches	Ten years								Eleven years							
	18 8	19 8	20 6	22 1	23 6	24 4	25 4	cm	19 6	20 9	21 6	23 1	24 6	25 4	26 7	cm
	7 4	7 8	8 1	8 7	9 3	9 6	10 0	in	7 7	8 2	8 5	9 1	9 7	10 0	10 5	in
47	40	43	44	48	52	53	56		43	45	47	51	55	57	59	
48	43	45	47	51	55	57	59		45	48	50	54	58	60	63	
49	45	48	50	54	58	60	63		49	52	54	59	64	66	69	
50	48	51	52	57	62	63	67		51	54	56	61	66	68	71	
51	49	52	54	59	64	66	69		53	56	58	63	68	70	73	
52	52	55	57	62	67	69	72		55	59	61	66	71	73	77	
53	55	59	61	66	71	73	77		58	61	64	69	74	77	80	
54	57	61	63	68	73	75	79		60	64	66	72	78	80	84	
55	60	64	66	72	78	80	84		64	68	70	76	82	84	88	
56	64	68	70	76	82	84	88		67	71	74	80	86	89	93	
57	67	71	74	80	86	89	93		71	75	78	84	90	93	97	
58	69	73	76	82	88	91	95		74	79	81	88	95	97	102	
59	72	76	78	85	92	94	98		78	83	86	93	100	103	108	
60	75	79	82	89	96	99	103		82	87	90	97	104	107	112	
61									86	91	94	102	110	113	118	
62																

*Weight in pounds (without clothing)

has small bones and should weigh less than a broad built child of the same age and height. The width-length index measures the bony framework or body build and provides the basis for calculating the deviation from average weight.

TABLE I—CONT'D

	Twelve years								Thirteen years							
	70.6 8.1	21.6 8.5	2.3 4.8	4.1 9.5	5.9 10.2	6.6 10.5	7.6 cm. 10.9 in.		1.3 8.4	2.6 8.9	3.3 9.2	5.1 9.9	26.9 10.6	27.6 10.9	28.9 cm. 11.4 in.	
Height in Inches	50	53	55	60	65	67	70		58	61	64	69	74	77	80	
	53	56	58	63	68	70	73		60	63	65	71	77	81	82	
	54	58	60	65	70	72	76		61	67	69	75	81	83	87	
	56	60	62	67	72	74	78		66	70	73	79	85	88	92	
	58	61	64	69	74	77	80		69	73	76	82	88	91	95	
	61	65	67	73	79	81	85		72	77	79	86	93	95	100	
	65	69	71	77	83	85	89		76	80	83	90	97	100	103	
	67	71	74	80	86	89	93		80	85	88	95	102	105	110	
	71	75	78	84	90	93	97		83	88	91	99	106	110	115	
	74	79	81	88	95	97	102		88	93	96	104	112	115	120	
	78	83	86	93	100	103	108		91	97	100	108	116	119	125	
	83	88	91	98	105	108	113		95	101	105	113	121	125	131	
	87	91	95	103	111	114	119		100	106	109	118	127	130	136	
	91	97	100	108	116	119	125		103	109	113	121	131	135	141	
	95	100	104	112	120	124	129		106	113	117	126	135	139	146	
	98	104	107	116	125	128	134		109	115	119	129	139	143	149	
	Fourteen years								Fifteen years							
	18.2 8.6	23.1 9.1	3.9 9.4	25.6 10.1	27.3 10.8	28.1 11.1	29.4 cm. 11.6 in.		2.1 8.8	23.6 9.3	4.4 9.6	26.1 10.3	28.0 11.0	28.8 11.3	30.0 cm. 11.8 in.	
Height in Inches	55	64	68	70	76	81	88		6	80	83	90	97	100	104	
	56	68	71	75	81	87	90		79	84	87	94	101	104	109	
	57	71	74	79	86	93	95		83	88	91	98	105	108	113	
	58	77	81	84	91	98	101		87	92	95	103	111	114	119	
	59	79	84	87	94	101	104		89	95	98	106	114	117	123	
	60	83	88	92	99	106	110		94	99	103	111	119	123	128	
	61	87	91	95	103	111	114		96	102	105	114	123	126	132	
	62	90	96	99	107	115	118		99	105	109	117	126	129	135	
	63	95	98	102	110	118	121		101	107	111	120	129	133	139	
	64	97	103	106	115	121	124		104	110	114	123	132	136	142	
	65	100	106	110	119	128	132		107	115	119	129	139	143	149	
	66	103	109	113	122	131	135		112	119	123	133	143	147	154	
	67	108	115	118	128	138	141		114	121	125	135	145	149	156	
	68	111	117	121	131	141	145		115	122	126	136	146	150	157	
	69	115	119	123	133	143	147		117	124	128	138	148	152	159	
	70	113	120	124	134	144	148									
	71	115	122	126	136	146	150									
	Sixteen years															
	22.9 9.0	4.1 9.5	24.9 9.8	26.6 10.5	28.4 11.2	29.2 11.5	30.5 cm. 12.0 in.									
Height in Inches	59	74	79	81	88	95	102									
	60	79	84	87	94	101	109									
	61	83	90	93	101	109	117									
	62	89	94	97	105	113	121									
	63	93	99	103	111	119	128									
	64	97	103	106	115	124	133									
	65	101	107	111	120	129	139									
	66	106	113	117	126	135	146									
	67	111	118	122	132	142	153									
	68	114	121	125	135	145	156									
	69	119	126	131	141	151	163									
	70	121	128	132	143	154	165									
	71	126	133	138	149	160	171									
	72	129	137	142	153	164	177									
	73	134	142	146	158	170	182									
	74	137	145	150	162	174	187									

Directions: Take age at nearest birthday and height at nearest inch. Measure the bi-iliac diameter and match it with the nearest diameter for the proper age shown along the top of the table. Appropriate weight for build is read for the given height at that width.

Weight in pounds (without clothing)

For the convenience of physicians we have constructed Tables I and II showing appropriate weights for body build based on the two physical traits, height and bicristal diameter, which Dr Gray found correlated most highly with weight, and taking into consideration age which correlated third. We have called these Width-Weight tables. The Baldwin-Wood table was used to determine average height and

TABLE II
WIDTH WEIGHT TABLE FOR BOYS*
SIX TO SIXTEEN YEARS

	Six years								Seven years							
	15 7 6 2	16 7 6 6	17 2 6 8	18 5 7 3	19 8 7 8	20 3 8 0	21 3 8 4 in		16 2 6 4	17 3 6 8	18 0 7 1	19 3 7 6	20 6 8 1	21 3 8 4	22 4 8 8 in	
38	26	28	29	32	35	36	38		30	32	33	36	39	40	42	
39	27	29	30	33	36	37	39		31	33	34	37	40	41	43	
40	28	30	31	34	37	38	40		32	34	36	39	41	44	46	
41	30	32	33	36	39	40	42		35	37	38	42	46	47	49	
42	31	33	34	37	40	41	43		37	39	40	44	48	49	51	
43	32	34	36	39	41	44	46		38	41	42	46	50	51	53	
44	35	37	38	42	46	47	49		40	43	44	48	52	53	56	
45	37	39	40	44	48	49	51		43	45	47	51	55	57	59	
46	38	41	42	46	50	51	53		44	47	49	53	57	59	62	
47	40	43	44	48	52	53	56		47	50	51	56	61	62	65	
48	42	44	46	50	54	56	58		49	52	54	59	64	66	69	
49	44	47	49	53	57	59	62		51	54	56	61	66	68	71	
50	46	49	51	55	59	61	63		54	57	59	64	69	71	74	
51																
52																
53																
54																
55																
56																
	Eight years								Nine years							
	17 2 6 8	18 3 7 2	18 8 7 4	20 3 8 0	21 8 8 6	22 3 8 8	23 4 9 2 in		18 1 7 1	19 1 7 5	19 6 7 7	21 1 8 3	22 6 8 9	23 1 9 1	24 1 9 5 in	
42	31	33	34	37	40	41	43		37	39	40	44	48	49	51	
43	32	34	36	39	41	44	46		38	41	42	46	50	51	53	
44	35	37	38	42	46	47	49		40	43	44	48	52	53	56	
45	37	39	40	44	48	49	51		43	45	47	51	55	57	59	
46	38	41	42	46	50	51	53		44	47	49	53	57	59	62	
47	40	43	44	48	52	53	56		47	50	51	56	61	62	65	
48	43	45	47	51	55	57	59		49	52	54	59	64	66	69	
49	44	47	49	53	57	59	62		52	55	57	62	67	69	72	
50	47	50	51	56	61	62	65		54	58	60	65	70	72	76	
51	49	52	54	59	64	66	69		57	61	63	68	73	75	79	
52	52	55	57	62	67	69	72		59	62	65	70	75	78	81	
53	54	58	60	65	70	72	76		62	66	68	74	80	82	86	
54	57	61	63	68	73	75	79		65	69	71	77	83	85	89	
55	59	62	65	70	75	78	81		68	72	75	81	87	90	94	
56	61	65	67	73	79	81	85									
57																
58																
	Ten years								Eleven years							
	18 3 7 2	19 3 7 6	20 1 7 9	21 6 8 5	23 1 9 1	23 9 9 4	24 9 9 8 in		19 0 7 5	20 0 7 9	20 8 8 2	22 3 8 8	23 8 9 4	24 6 9 7	25 6 10 1 in	
47	40	43	44	48	52	53	56		44	47	49	53	57	59	62	
48	43	45	47	51	55	57	59		47	50	51	56	61	62	65	
49	44	47	49	53	57	59	62		49	52	54	59	64	66	69	
50	47	50	51	56	61	62	65		52	55	57	62	67	69	72	
51	49	52	54	59	64	66	69		54	58	60	65	70	72	76	
52	52	55	57	62	67	69	72		57	61	63	68	73	75	79	
53	54	58	60	65	70	72	76		60	63	65	71	77	79	82	
54	57	61	63	68	73	75	79		63	67	69	75	81	83	87	
55	60	63	65	71	77	79	82		66	70	73	79	85	88	92	
56	63	67	69	75	81	83	87		69	73	76	82	88	91	95	
57	66	70	72	78	84	86	90		72	77	79	86	93	95	100	
58	69	73	76	82	88	91	95		76	80	83	90	97	100	104	
59	72	76	78	85	92	94	98		78	83	86	93	100	103	108	
60	75	79	82	89	96	99	103		83	88	91	98	105	108	113	
61									87	92	95	103	111	114	119	
62																
63																

*Weight in pounds (without clothing)

weight for each age sex group The Underweight Reference tables compiled by the American Child Health Association in 1924 were used to determine 7 10 15 per cent under average weight for each age and height. The percentages over average weight were calculated directly from these

TABLE II—CONT'D

Height in inches	Twelve years								Thirteen years							
	19 8	20 8	21 6	23 1	24 6	5 4	26 4	cm.	20 3	1 3	22 1	23 6	25 1	25 9	26 9	cm.
	7 8	8 2	8 5	9 1	9 7	10 0	10 4		8 0	8 4	8 7	9 3	9 9	10 2	10 6	n.
50	47	50	51	56	61	62	65		52	55	57	62	67	69	77	
51	49	52	54	59	64	66	69		55	59	61	66	71	73	77	
52	52	55	57	62	67	69	72		58	61	64	69	74	77	80	
53	55	59	61	66	71	73	77		60	64	66	72	78	80	84	
54	58	61	64	69	74	77	80		64	68	70	76	82	84	88	
55	60	64	66	71	78	80	84		67	71	74	80	86	89	93	
56	63	67	69	75	81	83	87		70	74	77	83	89	92	96	
57	66	70	73	79	85	88	9		73	78	80	87	94	96	101	
58	70	74	77	83	89	92	96		77	81	84	91	98	101	105	
59	73	78	80	87	94	96	101		80	85	88	95	102	105	110	
60	76	80	83	90	97	100	104		84	89	9	100	108	111	116	
61	79	84	87	94	101	104	109		89	94	97	105	113	116	121	
62	83	88	92	99	106	110	115		9	98	101	109	117	120	126	
63	88	93	96	104	11	115	120		97	103	106	115	124	127	133	
64	90	96	99	107	115	118	124		99	105	108	117	126	129	135	
65	95	100	104	112	120	124	129		101	109	113	1 2	131	135	141	
Height in inches	Fourteen years								Fifteen years							
	21 1	22 3	3 1	24 9	26 7	27 5	28 7	cm.	21 6	22 9	23 6	25 4	27 2	27 9	29	cm.
	8 3	8 8	9 1	9 8	10 5	10 8	11 3	in.	8 3	9 0	9 3	10 0	10 7	11 0	11 5	n.
54	59	62	65	70	75	78	81		66	70	7	78	84	86	90	
55	60	64	66	72	78	80	84		68	72	75	81	87	90	94	
56	64	68	70	76	82	84	88		7	76	78	85	9	94	98	
57	68	72	75	81	87	90	94		74	79	81	88	95	97	10	
58	71	75	78	84	90	93	97		78	83	86	93	100	103	108	
59	74	79	81	88	95	97	10		81	86	91	98	105	108	113	
60	77	8	85	9	99	102	107		85	91	94	102	110	113	118	
61	82	87	90	97	104	107	112		91	97	100	108	116	119	1 5	
62	85	90	93	101	109	112	117		95	101	105	113	121	1 5	131	
63	89	95	98	106	114	117	123		100	106	109	118	127	130	136	
64	94	99	101	111	119	121	128		104	110	114	123	132	136	14	
65	98	104	107	116	125	128	134		108	115	118	128	138	141	148	
66	101	107	111	120	129	133	139		111	118	122	132	142	146	153	
67	106	113	117	126	135	139	146		116	123	127	137	147	151	158	
68	111	118	122	132	142	146	153		120	127	133	142	152	157	164	
69	114	121	125	135	145	149	156		125	133	137	148	159	163	171	
70	119	126	131	141	151	156	163		128	135	140	151	162	167	174	
71	123	131	135	146	157	161	169		131	139	144	155	166	171	179	
72									134	142	146	158	170	174	182	
Height in inches	Sixteen years								Seventeen years							
	23	23 6	24 4	26 2	28 0	8 8	30 0	cm.	23	23 6	24 4	26 2	28 0	8 8	30 0	cm.
	8 8	9 3	9 6	10 3	11 0	11 5	11 8	in.	8 8	9 3	9 6	10 3	11 0	11 5	11 8	in.
59	74	79	81	88	95	97	102		66	70	7	78	84	86	90	
60	79	84	87	94	101	104	109		68	72	75	81	87	90	94	
61	85	90	93	101	109	11	117		7	76	78	85	9	94	98	
62	89	94	97	105	113	116	1 1		74	79	81	88	95	97	10	
63	94	99	101	111	119	123	128		78	83	86	93	100	103	108	
64	97	103	106	115	124	12	133		81	86	91	98	105	108	113	
65	101	108	111	120	129	133	139		85	91	94	102	110	113	118	
66	106	113	117	126	135	139	146		91	97	100	108	116	119	1 5	
67	111	118	1 2	132	142	146	153		95	101	105	113	121	1 5	131	
68	114	121	125	135	145	149	156		100	106	109	118	127	130	136	
69	119	127	131	141	151	156	163		104	110	114	123	132	136	14	
70	121	128	132	143	154	158	165		108	115	118	128	138	141	148	
71	126	134	138	149	160	165	172		111	118	122	132	142	146	153	
72	129	137	142	153	164	169	177		116	123	127	137	147	151	158	
73	134	14	146	158	170	174	182		120	127	133	142	152	157	164	
74	13	145	150	162	174	179	187		125	133	137	148	159	163	171	

Directly To be used to measure birth weight and height at nearest inch. Measure the bi-iliac diameter and match it with the nearest diameter for the proper sex shown along the top of the table. Appropriate weight for build read for the given height at that width.

Weight in pounds (without clothing)

The mean width-length index as calculated for each age sex group in our series was matched with the figures for the average height and average weight for each age sex group on the Baldwin-Wood table.* The 7 per cent underweight column from the Reference Table was matched with the figure for 7 per cent narrower than the mean of the width-length index for each age sex group, the 10 per cent underweight column was matched with the figure for 10 per cent narrower than the mean, and the 15 per cent underweight column was matched with the 15 per cent narrower than the mean of the width-length index. The over average weight columns were calculated in the same manner.

Since it seems cumbersome to print the width-length index with each weight the indices are omitted and only the width measurements are shown. The center width for each age and sex represents the mean of the measurements of the bi-iliac diameter for that age and sex in our series. The other widths are those from which the 7, 10, and 15 per cent variation indices were derived.

The Width-Weight tables offer seven normal weights for each height and age depending on the width of the iliac diameter. Since width measurements should be done next to the skin, the weights in the Baldwin-Wood table and from the American Child Health Underweight reference tables were corrected for clothes by subtracting one pound for heights 38 to 40 inches and two pounds for heights above 40 inches, as suggested in the Baldwin-Wood table. Our table is then a modification of the Baldwin-Wood table, taking width into consideration.

To use the Width-Weight table age is taken at the nearest birthday and height at the nearest inch. The actual bi-iliac diameter is matched with the nearest width measurement shown for the proper age sex group at the top of the table and the weight is read for the proper height at that width. Children who deviate very markedly from average, those too tall or too short, too broad or too narrow to be found on the table, should be considered individually.

*In preparing Tables I and II showing weight deviation in terms of width deviation the regression formula $y = (r \frac{\sigma_y}{\sigma_x})x$ was applied as suggested by Dr. R. L. Jenkins. When x equals the percentage deviation from the mean width-length index for the age sex group and y equals the percentage deviation from average weight for height age and sex as given in the Baldwin-Wood table application of the formula yields the following values:

	Ages				r_{xy}	$\frac{\sigma_y}{\sigma_x}$	
	6	7	8	9			
Male and Female					0.48	2.19	1.051
Male	10	11	12		0.63	1.59	1.007
Female	10	11	12		0.622	1.45	0.902
Male	13	14	15	16	0.46	1.85	0.951
Female	13	14	15	16	0.51	2.05	1.045

It appears then, that (within the limits of the tables presented in this paper) weight deviation varies in direct proportion to width deviation since y equals approximately 1.

TABLE III
 COMPARISON OF OLD AND NEW STANDARDS

SEX	AGE	PERCENTAGE DEVIATION FROM BALDWIN WOOD WEIGHT				PERCENTAGE DEVIATION FROM WEIGHT FOR BUILD				TOTAL DEVIATION BALDWIN WOOD WT	TOTAL DEVIATION WT FOR BUILD
		NO CASES	AVER. PLUS DEV	NO CASES	AVER. MINUS DEV	NO CASES	AVER. PLUS DEV	NO CASES	AVER. MINUS DEV		
M	4	0	11.7	4	7.7	5	7.0	0	5.1	+4.0	+2.8
F	4	2	10.8	2	6.0	3	9.8	1	5.0	+4.8	+4.8
M	5	3	11.0	3	8.4	4	7.2	2	10.1	+3.5	-2.0
F	5	7	11.4	13	10.4	7	6.0	13	8.8	+1.3	-1.9
M	6	7	8.7	29	8.4	7	7.0	21	6.4	0	+1.5
F	6	14	0.7	12	13.2	12	8.3	14	9.2	-3.5	-0.9
M	7	7	0.2	22	0.4	11	4.3	18	6.7	-8.2	-2.4
F	7	14	8.1	11	10.3	13	5.0	12	9.4	-2.2	-3.0
M	8	4	0.2	24	9.6	5	6.0	24	7.0	-4.4	-1.3
F	8	11	11.0	8	9.4	15	7.0	24	7.8	+1.7	-0.0
M	9	8	9.9	10	9.7	8	11.0	13	7.5	+0.2	+3.1
F	9	16	12.3	20	9.6	19	9.4	17	7.0	+2.8	+2.4
M	10	10	13.3	12	9.3	10	9.8	12	7.3	+4.0	+2.5
F	10	13	12.1	10	10.0	15	9.4	18	7.2	+1.0	+2.2
M	11	7	8.0	10	7.8	9	7.4	7	6.9	+0.8	+0.5
F	11	14	14.2	10	10.3	16	10.0	17	0.8	+3.9	+3.7
M	12	11	10.3	10	7.7	13	7.4	13	4.9	+2.6	+3.5
F	12	9	18.6	21	11.0	12	7.3	18	7.7	+7.0	-0.4
M	13	8	7.0	10	0.7	8	7.0	10	7.0	-1.8	+0.0
F	13	14	10.0	6	11.0	14	8.9	7	8.8	-0.5	+0.1
M	14	4	10.7	0	8.0	4	10.0	9	7.9	+1.0	+2.7
F	14	9	10.1	6	0.1	11	0.3	4	7.2	+4.0	-0.0
M	15	4	6.3	4	11.8	4	9.4	5	7.7	-6.5	-3.3
F	15	5	14.1	6	0.4	7	7.5	4	7.7	+4.7	-0.2
		207		318		32		207		71.5	48.1
		0 zero deviation 531 Cases Total				2 zero deviation				Total per cent deviation	

To test the superiority of the new width-weight tables over the original Baldwin-Wood tables the amount of deviation from each weight standard was measured on a series of 531 unselected healthy children. Table III shows the average amounts of deviation above and below the Baldwin-Wood normal and above and below the width-weight normal for each age and sex. Ages were distributed from four to fifteen years and deviations were measured in percentage of the normal.

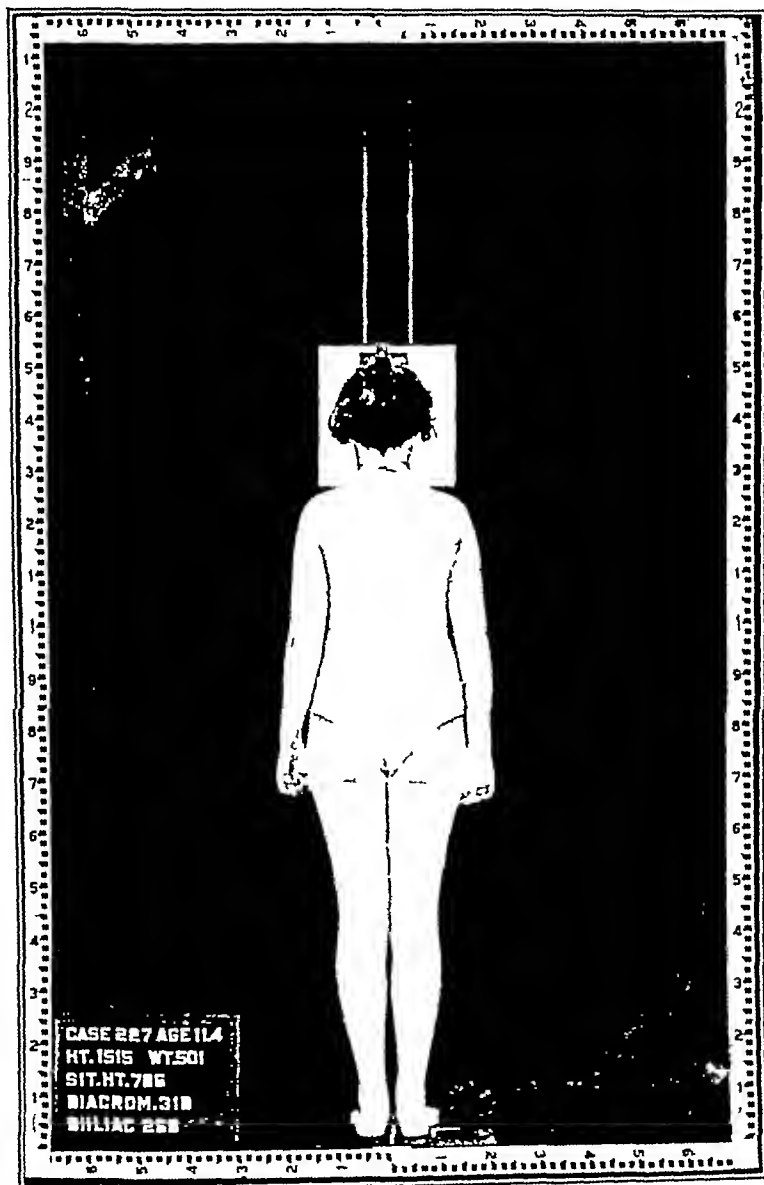


Fig 3—This girl is twenty-three per cent overweight by the standards of the Baldwin-Wood table, but since her width-height index is 10.7 per cent greater than the average for her age her weight is only 12.3 per cent above the average for her age, height, and skeletal build. (The measurements shown on the photograph are in millimeters and hectograms.)

The total group of children vary from the new table 48.1 per cent (0.090 per cent per child) as compared with 71.5 per cent from the Baldwin Wood (0.135 per cent per child)

For the general population as represented by the 531 unselected children the new width weight table fits 32.7 per cent better than the Baldwin Wood table

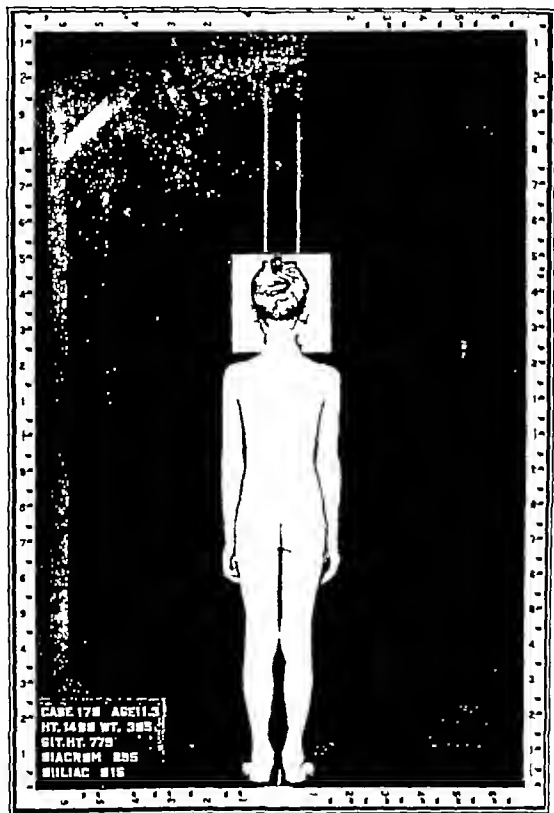


Fig. 4.—This boy is fifteen per cent underweight by the standards of the Baldwin-Wood table, but since his width height index is 7.7 per cent less than the average for his age his weight is only 7.3 per cent below the average for his age, height, and skeletal build. (The measurements shown on the photograph are in millimeters and hectograms.)

TABLE IV
WIDTH LENGTH INDICES
(Bia iliac Diameter in Inches)

Height in Inches	177	183	190	196	203	209	216	221	229	234	241	246	254	259	267	272	279	285	292	297	305	cm
	70	72	75	77	80	82	85	87	90	92	95	97	100	102	105	107	110	112	115	117	120	inches
44	161	165	170	174	181	187	192	196	203													
45	157	162	166	170	177	183	188	192	197													
46	154	158	162	167	173	179	184	188	195													
47	151	155	159	163	170	176	180	184	190	197												
48	148	152	156	160	166	172	176	180	186	193	197											
49	145	149	153	157	163	168	173	177	183	189	193	197										
50	142	146	150	154	160	165	169	173	179	185	189	193	199									
51	139	143	147	151	156	162	166	170	176	181	185	189	195	201								
52	136	140	144	148	153	159	163	167	172	178	182	186	191	197	201							
53	134	138	141	145	150	156	160	164	167	171	175	178	182	188	194	197						
54	131	135	139	142	148	153	157	161	166	172	175	179	184	190	193	197						
55		130		140	145	151	154	158	163	168	172	176	181	186	190	194	199					
56			137	147	152	158	161	165	170	175	179	183	188	193	197	201	197					
57			135	145	150	156	160	164	169	174	178	182	187	192	197	201	197					
58			133	143	148	154	158	162	167	172	176	180	185	190	194	197	201	197				
59				140	145	151	155	159	164	169	173	177	182	186	191	195	199	194				
60					147	153	157	161	166	171	175	179	184	189	193	197	201	196				
61					144	150	154	158	163	168	172	176	181	186	190	194	199	194				
62					141	147	151	155	160	165	169	173	178	183	187	191	196	191				
63					138	144	148	152	157	162	166	170	175	180	184	188	193	188				
64					135	141	145	149	154	159	163	168	173	177	181	185	190	185				
65					132	138	142	146	151	156	160	165	170	174	178	183	188	183				
66					129	135	140	144	149	153	158	163	168	173	177	181	186	181				
67					126	132	137	141	146	150	155	160	165	170	174	178	183	178				

TABLE V

MEAN WIDTH LENGTH INDEXES FOR SCHOOL CHILDREN ARRANGED BY SEX AND AGE

Age in years	6	7	8	9	10	11	12	13	14	15	16
Index Boys	139	158	158	159	158	157	157	156	155	154	154
Girls	159	159	159	159	160	161	162	163	163	164	164

TABLE VI

PERCENTAGE DEVIATION CORRESPONDING TO EACH UNIT OF DEVIATION FROM THE MEAN WIDTH LENGTH INDEX

WIDTH LENGTH INDEX	PERCENT DEVIATIONS FROM AVERAGE INDEX FOR EACH UNIT OF DEVIATION									
	1	2	3	4	5	6	7	8	9	10
150 153	0	1.3	2.0	2.4	3.3	4.0	4.6	5.3	6.0	6.6
154 157	0.6	1.3	1.9	2.6	3.2	3.9	4.5	5.1	5.8	6.4
158 161	0.6	1.3	1.9	2.5	3.1	3.7	4.4	5.0	5.6	6.3
162 165	0.6	1.2	1.8	2.4	3.1	3.7	4.3	4.9	5.5	6.1
166 169	0.6	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0
170 175	0.6	1.2	1.7	2.3	2.9	3.5	4.1	4.7	5.2	5.8

Example. The mean width length index for eleven year-old girls is 161 (See Table V). For a girl of this age whose index is 166 the unit deviation is 5 and the percentage of deviation is 3.1 per cent. She is 3.1 per cent broader for her height than the average for girls of her age.

Table IV is included for the convenience of those who are interested in finding the width length index. The bi-iliac diameter is found along the top and the standing height in the left hand column. The width length index appears where the two columns intersect.

Mean width length indexes for our 4560 children by age and sex are shown in Table V. The width length index for each child should be compared with the mean in this table, his percentage deviation may then be found by consulting Table VI. To use this device determine the difference between the child's width length index (found on Table IV) from the mean for his age and sex (found on Table V). Locate this difference along the top line of Table VI. Then find the mean width length index for age and sex in the left hand column of Table VI. The percentage deviation appears where the two columns intersect. This percentage deviation may be read as 8 per cent narrower than average or 12 per cent broader than average for age and sex. Since percentage deviation in weight from the Baldwin Wood table allowed for body build is equal to the percentage deviation found on Table VI the child who is 8 per cent narrower than average may weigh 8 per cent less than the weight assigned by the Baldwin Wood table for his age and height. The child found to be 12 per cent broader than average may weigh 12 per cent more than the weight assigned on the Baldwin Wood table.

In the rare cases where the percentage deviations from the width length index are more than 15 per cent an individual judgment should be made although the principle of the relationship between width and weight is still applicable. If the table were extended to cover wider deviations from average it would become too large and the chances

of inaccuracy would be greater since extreme deviations would be based on too few cases. The probability curve for deviation of normal persons from zero shows that there is one chance in about 150 of a deviation of 17 per cent and only one chance in about 500 of a deviation of 20 per cent.

SUMMARY

- 1 Nutritional status remains the best single criterion of health
- 2 Relative width of the body, or body build, should be considered in judging appropriate weight for age and sex
- 3 The relationship of body width to weight has been analyzed by mathematical correlation, using the measurements of 4560 school children
- 4 A simple method of measuring body build has been used to help determine appropriate weight
- 5 The four traits found to have the highest mathematical correlation with body weight are combined in new tables of appropriate weights for children aged six to sixteen years
- 6 The new tables fit the general population much better than the Baldwin-Wood tables when deviations from both standards are compared for 531 children

REFERENCES

- 1 Gray, Horace. *Biometrika* 20a 299, 1928, idem *Growth in Private School Children*, University of Chicago Press, 1931
- 2 Franzen, R. *Physical Measures of Growth and Nutrition*, American Child Health Association, 1929
- 3 Miles, W. R. *Science* 382, Oct. 19, 1928
- 4 Faber, H. K. *Am J Dis Child* 30 328, 1925
- 5 Dublin, L. I., and Gebhart, J. C. *New York Assoc for Improving the Condition of the Poor*, 1924
- 6 Turner, C. E. *Pub Mass Inst Tech Serial No* 20, June, 1931
- 7 Clark, T., Sydenstricker, E., and Collins, S. D. *Pub Health Rep* 39 518, 1924
- 8 Lucas, W. P., and Pryor, Helen B. *J A M A* 97 1127, 1931
- 9 Hrdlicka, A. *Anthropometry*, Philadelphia, 1920, Wistar Inst
- 10 Todd, T. W., and Lindala, A. *Am J Anat* 41 153, 1928
- 11 Dahlberg, G. *Twin Births and Twins from a Hereditary Point of View*, Stockholm, 1926

HEREDITARY ATAXIA

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BROUSSEE gave the name of Friedreich's disease to the symptom complex described by the Heidelberg clinician in 1863¹. This disease was characterized by onset during childhood, ataxia, loss of the patellar reflex, nystagmus, pes equinus, a slowly progressive course and its occurrence in members of the same family.

The existence of this clinical picture was confirmed in a large number of publications but it was soon found that the disease was not as sharply defined as at first described. Marie described a condition in young adults that had many points in common with the symptom complex of Friedreich, but differed in that there was a later onset, greater uncertainty in the gait, the tendon reflexes were present or exaggerated, there were ocular palsies and occasionally atrophy of the optic nerve. The existence of this clinical picture was confirmed by a number of observers and then cases were discovered combining symptoms of both diseases.

Most clinicians have come to the conclusion, in view of these facts, that Friedreich's disease and Marie's cerebellar ataxia can no longer be separated into two distinct groups either clinically or pathologically, and that it is more correct to include both of these conditions under the head of hereditary ataxia with preponderance of the spinal symptoms in some cases and of the cerebellar symptoms in others.

The spinal form of hereditary ataxia appears in the first decade of life as a rule, while the cerebellar form shows the first symptoms usually after the age of twenty. However, there is no constant difference between the spinal and cerebellar forms as regards the age when the disease first makes its appearance. The outstanding symptom of the cerebellar form of hereditary ataxia is the uncertainty of the gait. The disturbance of coordination affects not only the walking but also the standing and sitting postures. The motor unrest is not confined to the legs and early involves other portions of the body producing wobbling of the head, tremor of the hands, and ataxia of the arms.

Peculiar postures of the feet are often found in the spinal form of hereditary ataxia. The malformations are caused by an over extension of the large toe which may be an early symptom. As a rule it is followed by a further malformation of the foot and clawlike position of the toes. Roentgenograms do not show anomalies of the skeleton.

It is interesting to note that as a rule either the male members or the female members of a family are exclusively attacked. However, there appears to be no difference between the sexes as regards frequency.

The behavior of the patellar reflex is not constant. As a rule, the patellar reflex disappears early in the spinal form of hereditary ataxia and is exaggerated in the cerebellar form, but there are spinal forms of the disease with exaggerated patellar reflexes and cerebellar forms of the disease with diminished reflexes.

When the spinal form of hereditary ataxia has existed for some time there is a scoliosis or kyphoscoliosis, due to the weakness of the spinal muscles.

A series of important cerebral symptoms frequently accompany hereditary ataxia. Nystagmus is common in the spinal form and occasionally absent in the cerebellar type. Disturbance of the ocular muscles, such as strabismus, ptosis, and diplopia, have been observed in the cerebellar type. Optic atrophy is frequently present. The pupils are normal.

Speech might be compared to the gait in that it is slow and sometimes scanning. The speech defect usually increases with the severity of the disease. The intellect is also impaired in the spinal form. There may be a few infrequent symptoms, such as profuse salivation and forced laughter.

It was formerly thought that in hereditary ataxia there were few if any sensory changes, but in the light of later case reports with anatomic studies this view has been changed.

The problem which the disease presents is not so much the distribution of the lesions with the resulting clinical picture as the causation and exact nature of the affection. The following case report is given and the literature briefly reviewed in order to help further determine, if possible, the nature of hereditary ataxia.

CASE REPORT

M. Y., white female child, three and a half years old, was born November 21, 1927. At this time her father was twenty-nine years of age and her mother twenty-five years of age. There were two older children, a girl of six years and a girl of two years, both apparently well. The mother had one miscarriage at four months between the first and second child.

The father's mother at the age of thirty-five developed an ataxia and eventually had to be placed in a hospital. The father died a few months after the patient was born.

The mother's health was good while she was carrying the patient. Birth was normal at full term, and the infant weighed nine pounds and twelve ounces. Feeding had to be supplementary.

At the age of five months the mother noticed that while the infant had developed remarkably well physically she could not hold her head up. Because the child was so clumsy the mother thought she was just lazy. At six months the infant could hold her bottle. The child continued to gain but did not improve mentally. She was seen by several physicians who informed the mother that the child had a birth injury.

At the age of two and a half years the child was beginning to sit alone and could hold her bottle. She weighed 35 pounds. At this time she developed an acute illness with fever and an eruption which the mother says looked very much like

menstruation but her doctor diagnosed as scarlet fever. She was quite ill at this time lost much weight and was very weak. She gradually recovered but it was now noticed that when the child reached for her bottle she would grope something that she had not done before. In addition it was noticed that she was 'wobbly'. Except for this one illness the child had been well.

There have been no inoculations or vaccination.

On physical examination the child was seen to be obviously defective mentally. She was quite chubby her height was 35 in. and weight 38 pounds. The temperature was normal. The child would occasionally grimace and roll her head to one side or the other. She would roll her body and the spine was quite bowed. She was unable to walk.



FIG. 1

The face showed but little expression. The hair showed nothing unusual and the scalp was apparently normal.

The eyes showed no strabismus or nystagmus. She would follow her bottle and a light. The pupils were regular, equal and reacted to light. Ophthalmoscopic examination showed a slight increase in paleness on the nasal side of the optic nerve.

The teeth and gums were normal.

The spine showed a kyphoscoliosis. There was considerable weakness of the spinal muscles.

The heart and lungs were normal.

The abdomen was rather flabby. The spleen and liver were not palpable.

The lower extremities showed a great deal of flabby tissue with poorly developed muscles. Motion was considerably restricted. When supported, the child kept the legs together though there was no abductor spasm. There was dorsiflexion of the large toes.



Fig 2



Fig 3

The child had fair use of the arms with marked ataxia and could hold her bottle. Muscle development was only fair.

The neurologic examination of the cranial nerves showed no abnormalities.

There was some weakness of the muscles of the trunk resulting in the kyphoscoliosis. The child could not crawl or walk and when sitting down was ataxic and would gradually roll over on her back to nurse her bottle.

The biceps, triceps, patellar and ankle reflexes were hyperactive. Plantar stimulation gave dorsiflexion of the large toe.

Sensitivity was apparently normal.

The blood Wassermann was negative. Spinal puncture was not done.

PATHOLOGY

The changes in the posterior columns are the most definite and invariable features of hereditary ataxia being essentially a systemic degeneration with neuroglial proliferation of the dorsal column. The disease process is not confined to the posterior columns but is more diffused with the causation quite obscure. The tracts most commonly involved are the crossed pyramidal tracts, the columns of Goll and Burdach, Gower's tract, the direct cerebellar tract, and, in some instances, Lissauer's tract and the column of Clark. In the upper part of the cord the degeneration, as a rule, is not so pronounced but in the lumbar and sacral regions the degeneration involves almost completely the dorsal column.

A number of reported cases record no sensory disturbances. This paradox of preservation of sensation with pronounced degeneration of the posterior columns has been variously explained. Friedreich¹ said that the dorsal columns could not be the principal sensory tracts. Muller² came to the conclusion that the sensory impulses were conducted by naked axis cylinders within the degenerated tracts. Dejerine³ thought that sensation was not affected by degeneration in the columns of Goll and that alterations in the posterior columns may exist without sensory changes. Mott⁴ claims that the neurons consisting of small cells and fine fibers which subserve cutaneous sensory and viscerovascular functions, are not affected in Friedreich's disease as in tabes dorsalis and in consequence there are no visceral disturbances or loss of cutaneous sensibility. Pfeiffer⁵ believes the characteristic sensory loss when found in Friedreich's ataxia is an essential rather than an exceptional feature in the symptomatology of the disease. He points out that when the forms of sensibility transmitted by the dorsal columns are impaired with only moderate ataxia, the degeneration affects principally the posterior tracts, but when sensory loss is slight in proportion to the ataxia the spinocerebellar tracts are affected more intensely than the dorsal column tracts.

DISCUSSION

The causation of hereditary ataxia is obscure and has given rise to a variety of theories. The fact that it occurs in several children of

the same family at once suggests some obscure familial defect, but the additional fact that numerous brothers and sisters often escape indicates that the cause, whatever it is, is strangely limited or selective in its action. Gower's theory that the disease is due to an abiotrophy, or developmental defect, has been received with some favor.

Williamson⁶ suggested that the location of the lesions in the posterolateral regions of the cord may be due to a less adequate blood supply, the supposition being that the local resistive power is less. These regions receive their blood supply from small meningeal branches instead of the deep central artery as in the anterior and central parts of the cord.

That the disease first makes its appearance with an acute infection is well recorded. Hess' reporting case histories of twin boys developing Friedreich's ataxia after an attack of influenza in 1918 raised the question as to whether he was dealing with boys with a normal mental and physical system who had undergone an acute infection of the nervous system resulting in degeneration and scoliosis, or whether the acute infection resulted in degenerations in congenitally defective nervous systems, and came to the conclusion that he was dealing with Friedreich's ataxia. Lloyd and Newcomer⁸ report two children, of the same family and of the negro race, with indications of an unstable nervous system, the younger of whom developed ataxia at the age of six when he was recovering from typhoid fever. The development of ataxia in the present patient who obviously had a poor mental pattern was immediately preceded by an acute infection.

SUMMARY

A case of hereditary ataxia of the mixed type occurring after an acute infection in a white female child of two and a half years is reported.

The child in question had an obviously defective mental pattern.

CONCLUSION

Evidence is presented that given a congenitally defective nervous system in a child an acute infection can initiate a degenerative process of the dorsal columns of the spinal cord.

REFERENCES

1. Friedreich. *Virchows Arch f path Anat* 26:27-391, 1863, *ibid* 68:145, 1876, *ibid* 70:140, 1877.
2. Muller. *Deutsche Ztschr f Nervenb* 32:137, 1907.
3. Dejerine. *Med mod* 1:477, 1890, *Rev Neurol* 15:41, 1907.
4. Mott. *Arch Neurol from the Path Lab of the London County Asylums* 3:180, 1907.
5. Pfeiffer, J. A. F. *Arch Neurol & Psychiat* 7:341, 1922.
6. Williamson. *Diseases of the Spinal Cord*, New York, Oxford University Press, 1919.
7. Hess, Julius H. *N Clin North America* 5:1749, 1922.
8. Lloyd, James Hendrie, and Newcomer, Harry S. *Arch Neurol & Psychiat* 6:157, 1921.

VIRILISM AND HYPERTENSION IN INFANCY ASSOCIATED WITH ADRENAL TUMOR

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VIRILISM associated with adrenal tumor has been frequently reported. Lesions of the pituitary may apparently produce a similar picture but Cushing's syndrome¹ attributed to pituitary basophilism does not appear to include the changes in external genitals so striking in adrenal subjects and has been more often encountered in its extreme form in young adults. In an attempt to explain the similarity of signs produced by lesions of the anterior lobe of the pituitary and the suprarenal cortex Landon Brown² calls attention to the fact that both of these glands are in close association with nervous structures, the adrenal medulla being developed from sympathetic ganglion cells and the pituitary connected with the hypothalamus.

Renal hypernephroma apparently more common in later life is not believed to produce any alteration in sexual characteristics. A small number of malignant tumors of the ovary are accompanied by premature sexual development which according to Frank³ must be ascribed to the influence of the ovarian growth because of the fact that recession of the prematurity takes place after the removal of the tumor naturally no virilism would result. Pineal tumors although they may cause sexual precocity and obesity are not known to cause virilism. They apparently occur far more frequently in boys.

The case to be reported is unfortunately incomplete in that no autopsy was permitted and therefore no opportunity to examine the head postmortem. The very small sella turcica appearing in the x-ray film, however, strongly suggests the nonparticipation of the pituitary. The suprarenal factor was definitely demonstrated at operation the manifestations being those expected from a suprarenal growth occurring in infancy: obesity, precocious development, hirsuties, voice change, virilism, and marked hypertrophy of the clitoris and external genitals together with hypertension and cardiac enlargement.

The infant two years and two weeks old and of Italian parentage entered the Pediatric Department of the Ellis Hospital on March 11 1933. She was brought in by the parents, who feared a convulsion with the history of having had convulsions on and off ever since birth. On the day of admission she had become very cyanotic. There is a very indefinite history of mild degrees of precocity in two related children: one a cousin. The father is exceptionally dark and virile in appearance the mother large, dark and handsome rather than pretty.

Development was described as normal up to the end of the ninth month. She was mentally alert sat up, walked, talked and cut her teeth at the usual age periods.

but at nine months she began to gain weight very rapidly and a dark growth of hair was noticed all over the body

The infant was well supplied with subcutaneous fat, especially about breasts, shoulders, and face, her weight was $38\frac{1}{2}$ pounds, her features were masculine, and

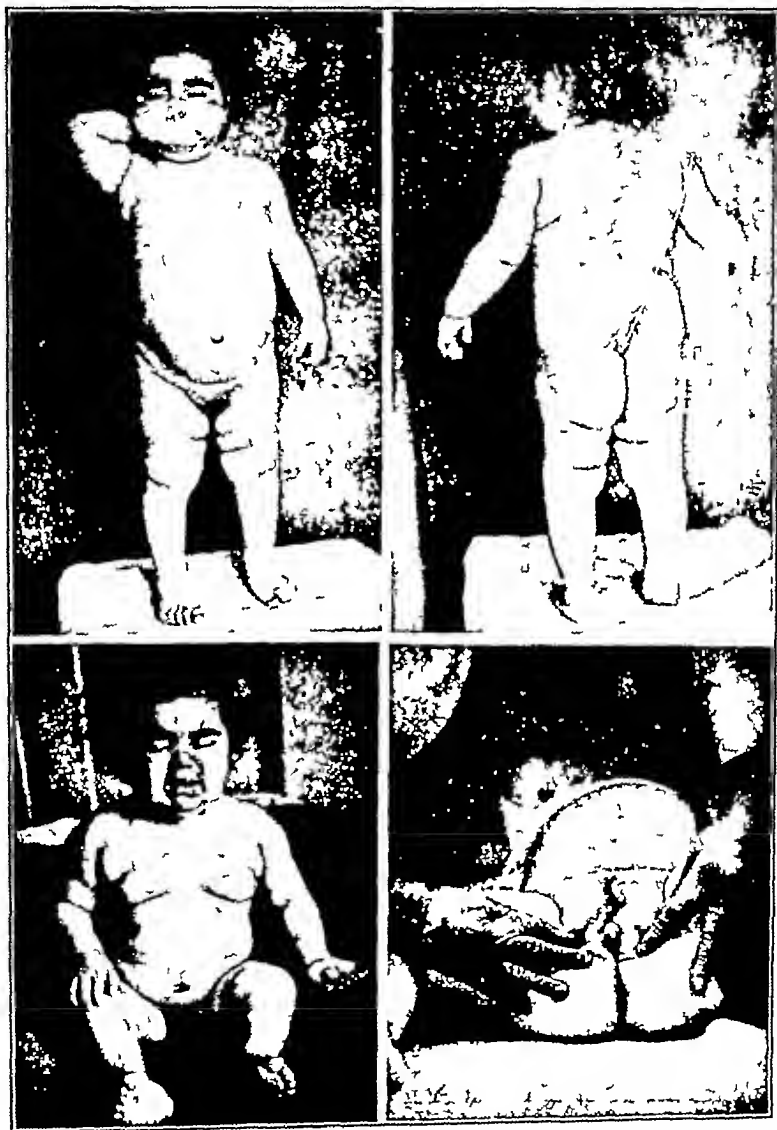


Fig 1—General appearance of child showing growth of hair and enlarged clitoris

she had a profuse growth of black hair on the back and pubic region, heavy eye brows, and a rather definite mustache. The scalp hair was abnormally heavy and extended onto the face. Her dental formula was normal for her age. A papular rash and some pigmentation of skin were noted. Most striking was the development of external genitals: enormous hypertrophy of the clitoris, prominent vulvae, and a

dense growth of pubic hair the vagina pervious and the urethra in the normal position in relation to vagina and clitoris.

Physical examination showed the heart evidently enlarged to the left and a mass could be felt in the right abdomen or at least a distinct difference in the two sides was evident upon percussion and palpation although study of the abdomen was rendered exceedingly difficult by the heart. Blood pressure registered 160/110 and the otygonnds were reported as showing evidence of hypertension. Dr. Park, who made the ophthalmoscopic studies reported tortuosity of the blood vessels similar to that found in cases of high blood pressure before learning of our pressure findings.



Fig. —X ray of skull showing small sella turcica.

X ray of the skull taken laterally showed nothing other than a sella turcica which appeared extremely small. This might be interpreted as indicating a small pituitary but it is only fair to note that the significance of this finding has been questioned. The thickness and contour of the cranium seemed normal for a child of that age. The heart shadow was extremely large in keeping with the blood pressure and confirming the physical findings. A more than normal opacity in the right abdomen seemed to give additional confirmation to the diagnosis of right adrenal tumor. A ragged appearance of the lower epiphyses of the femora was demonstrated. Hairiness of the clinoid processes has been noted in two cases quoted by Langdon Brown as apparently due to deficiency of calcium salts. Several examinations of the urine

revealed only a large amount of amorphous material and a very faint trace of albumin, sugar was always absent, no blood was found, the number of leucocytes insignificant

Blood Wassermann and Kahn tests were negative Blood sugar 136 mg per 100 c.c., possibly somewhat high, erythrocytes and hemoglobin low, with a leucocytosis of 24,000 two days before operation

The patient was operated on the eighth day in the hospital by Dr Stanton, and I quote from his record Uterus apparently normal for age Ovaries (estimated) $1 \times 4 \times 3$ cm, equal in size Both adrenals were large, the left smaller than the right which was adherent to the liver and measured approximately 9 by 6 by 7 centimeters, and so soft that it indicated malignancy, both were separate from the kidneys The right adrenal was shelled out subcortically Very little hemorrhage was reported at operation, although there was some oozing from the incision later Death occurred within thirty six hours.

No postmortem study was possible other than examination of the tumor mass by Dr Ellis Kellert Its weight was reported as 79.7 gm, the specimens consist



Fig 3—X ray of chest, showing enlargement of heart.

ing of several masses of pale yellow, blood stained, fatlike tissue, extremely ragged and irregular in shape, the largest piece measuring 6 by 4.5 by 3 cm This piece, on section, was seen to consist of soft hemorrhagic tissue somewhat resembling dark red blood clot at the margins of which was soft, grayish tissue Dr Kellert reported that sections showed a cellular tumor together with extensive areas of necrotic tumor tissue and hemorrhage, the tumor cells large, poorly defined, and varying greatly in size They appeared to be somewhat rounded and contained vacuolated cytoplasm The nuclei varied greatly in size, many macronuclei and all stages of chromatic change being present Certain cells contained several nuclei and others nuclear figures The cells showed no definite arrangement but there was a slight tendency to grow in columns Very little stroma was present Anatomical diagnosis Adrenal carcinoma

The case is of the cortical type with definite, easily interpreted syndrome, although lesions of the pituitary and pineal must be excluded as causative factors Tumors of medullary origin of the type first

described by Hutchinson produce only vague symptoms referable to the abdomen until the characteristic movement of the skull occurs, their early diagnosis seems rarely possible although Peterman,⁴ commenting upon a case of his own states that tumors of the right suprarenal gland usually produce abdominal pain and thus direct attention to their presence.

In a recent number of the *Journal of Surgery* Leblond⁵ of the University of Virginia writes of a cortical adrenal tumor removed from an infant of eleven months by William F. Hartlett of St. Louis. A description of this case was published in 1917 and commented upon as distinctive among undifferentiated tumors as the first case successfully operated upon. The child was alive and in perfect health fifteen years later. Collett's case⁶ operated upon in 1921 was at that time believed to be the first to recover although recovery was not complete, all signs of virilism having not yet disappeared after two years. This case is especially interesting in that an indirect laryngoscopic examination revealed the vocal cords unusually long and broad almost as in an adult male. Nine years later Harris and Plewes reported theirs as the second successful case.

Probably the youngest recorded case is that of Lightwood,⁷ a male infant of eighteen weeks. The appearance of the baby was described as peculiar on account of the visible hard deposits of fat in the cheeks and around shoulders and scapulae. There was a florid color of the face and the hair on the head was plentiful with slight growth on the forehead but no development of hair elsewhere. A mass was felt in the left flank which appeared larger and lower than a normal left kidney. Pneumonia developed and death occurred eleven days after admission to the hospital. The tumor was demonstrated at autopsy.

In the last few years the results of surgical removal have been most encouraging though certainly dependent in malignancy upon early recognition before metastasis has occurred. Cecil's recent statistics⁸ show that all the cases that had cortical hyperplasia and adenoma excepting where congenital recovered from the operation and also were cured of the disease with loss of abnormal distribution of hair and fat and recession of the clitoris to normal. Twenty-two per cent of the patients with hypernephroma completely recovered. Since most of the fatalities occurred within a few hours after operation a technic designed to prevent shock is essential. Cecil advises tying of the vessels particularly the veins before manipulating the tumor to obviate the danger of metastases of detached particles and to prevent a large amount of secretion from being suddenly squeezed into the circulation. It is imperative to know that the corresponding gland is functioning.

REFERENCES

- 1 Cushing, Harvey J A M A 99 281, 1932
- 2 Brown, W Langdon The Endocrine in General Medicine, New York, 1927, Paul
B Hoeber
- 3 Frank, Robert T Am J Dis Child 43 942, 1932
- 4 Peterman, M G Am J Dis Child 43 655, 1932
- 5 Lehman, E P Ann Surg 95 473, 1932
- 6 Collett, Arthur Am J Dis Child 27 204, 1924
- 7 Lightwood, Reginald Arch Dis Childhood 7 37, 1932
- 8 Cecil, Howard L J A M A 100 463, 1933

THE TREATMENT OF PERTUSSIS WITH GOLD TRIBROMIDE

REPORT OF SEVENTY FIVE CASES

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NEW YORK

PERTUSSIS is one of the common communicable diseases of childhood affecting all races in all climates. It varies greatly in its epidemiology, virulence and seasonal prevalence. Since the disease is universal and there is only a slight natural immunity to it, the number of whooping cough cases must be very large. The death rate from whooping cough per 100,000 population in the registration area in the United States for the last thirty years averages 9.92. The younger the child, the greater the mortality. The number of children in the United States dying from pertussis and its complications is estimated to be about 25,000 a year.

History—In all probability, whooping cough was known to the early Greek, Roman, and Arabian physicians and to the physicians of the middle ages. The first epidemic of pertussis occurred in Paris in 1578 and was described by Ballonius. The second epidemic occurred in London in 1658 and was recorded by Thomas Willis. Sydenham described the disease more fully in 1670 and again in 1679. Pertussis appeared in Germany in epidemic form in 1724. During a general epidemic which spread throughout Europe in 1732 the disease was carried to America.

Etiology—An organism of the influenza group which is known as the *Bacillus pertussis* or the Bordet Gengou bacillus has been generally accepted as the etiologic agent of whooping cough. A great deal of doubt has recently been cast on the etiologic relationship of this organism to pertussis. Much research work is in progress on the etiology of whooping cough and some filtrable virus may be found to be the real cause of this universal disease.

Anatomic and Physiologic Pathology—The chief anatomic pathologic condition in pertussis is a catarrhal inflammation of the upper respiratory tract with degeneration of the ciliated epithelium. The mucous membrane secretes a thick, whitish, tenacious substance consisting chiefly of mucus, epithelial cells, leucocytes, and microorganisms. The submucosa is swollen and edematous and there is in many cases, a peribronchitis with a peribronchiolitis. There may be other pathologic conditions affecting various organs as a result of the toxemia or the physical violence due to the stress and strain of coughing. The physiologic pathology is characterized by a hyperirritability of the cough center. The toxemia of whooping cough lowers the threshold of the cough

center so that the slightest central or peripheral irritation causes a shower of coughing spasms. The proximity of the coughing center to the respiratory and the vomiting centers accounts for the respiratory distress and the frequent vomiting in pertussis.

Diagnosis—In the majority of cases, there is no difficulty in making a correct clinical diagnosis of pertussis. A bacteriologic, hematologic, or serologic diagnosis is of value in doubtful cases. A history of exposure to the disease, a persistent paroxysmal cough with a tendency to be worse at night, a negative finding on physical examination, and an apparently well child between the paroxysms are indicative of whooping cough.

TREATMENT

During the middle ages, and even up to the seventeenth century, whooping cough was treated with irrational folk-remedies. Later various herbs were highly recommended. At the present time, a large number of drugs are being used with poor therapeutic results. Vaccines have been used for some years with gradually diminishing enthusiasm. Convalescent blood serum has been tried and discarded. Ether, given intramuscularly or by rectum, has been in vogue for some time, but has proved of little value and much discomfort. X-ray treatments over the chests of whooping cough patients have been tried but have not gained much therapeutic popularity. Carbon dioxide inhalation was recently suggested but its practical application is difficult in general everyday practice.

In an effort to find some reliable medicine for the treatment of pertussis, I began several years ago the study of the therapeutic effect of the anti-whooping cough drugs in common use. I divided them as nearly as possible, into hypnotics, sedatives, and antispasmodics and gave each group a careful and thorough trial in a fairly large number of cases. The results were not encouraging. I then made a special study of the bromides and classified them into monobromides or univalents, dibromides or bivalents, and tribromides or trivalents. Potassium bromide (KBr), sodium bromide (NaBr), lithium bromide (LiBr), and ammonium bromide (NH_4Br) are univalent bromides. Calcium bromide (CaBr_2) and strontium bromide (SrBr_2) are bivalent bromides. Gold bromide (AuBr_3), iron bromide (FeBr_3 or Fe_2Br_6), arsenic bromide (AsBr_3), and aluminum bromide (AlBr_3) are trivalent bromides. In observing the action of the bromides, I found that the dibromides gave better sedative or bromine action than the monobromides and the tribromides were more effective than the monobromides or the dibromides. Of the tribromides, the most suitable preparation for medicinal purposes is gold tribromide. This drug I have used in whooping cough for the last four years with satisfactory results.

In the therapeutic study of gold in whooping cough I used the neutral salt of gold tribromide. This is a compound of gold and hydrobromic acid which has no free acid. It is brownish black in color, deliquescent and soluble in water. Its gold content is about 45 per cent. This chemical is to be distinguished from acid bromauric N F which is an acid salt of gold and hydrobromic acid with some free acid. It is reddish brown, unstable, very deliquescent, and freely soluble in water. It contains about 32 per cent of gold.

The pharmacologic action and the therapeutic effect of gold tribromide in pertussis is probably due to a specific chemical reaction between the gold and the tribromine ions with the formation of a compound which has neurosedative, antispasmodic and antibacterial action. The compound of gold tribromide reduces the reflex irritability of the cough center and causes general sedative and antispasmodic effect. It shortens the period of the illness, diminishes the number and severity of the paroxysms, and prevents complications.

Treatment consisted in the administration by mouth of a solution of gold tribromide in water. The dosage varied with the age of the child and the severity of the paroxysmal cough. As a general rule $\frac{1}{20}$ to $\frac{1}{10}$ of a grain three times a day after meals and once at mid night was given. It was found however that a solution of gold tribromide in water did not keep well on standing for some time. There were frequently some slight chemical changes with a sedimentation due probably to oxidation. To avoid using an unstable medication I am now prescribing a uniform stable palpable preparation known as Elixir gold tribromide (Elixir bromaurate)*. The dosage is a teaspoonful three or four times a day after meals.

Result of Treatment—The result of treatment in 75 whooping cough cases during the last four years was most encouraging. Of the 75 patients, there were 43 females and 32 males, the ages ranging from two weeks to eight years. There were 2 adult cases. In about two thirds of the whooping cough patients the cough subsided in three weeks, in the others it abated within from five to seven weeks. In all cases after three or four days treatment with gold tribromide the cough was less frequent and less distressing, the attacks were shorter and milder, the vomiting ceased and the sleep was more restful. There were no recurrences, complications or fatalities in this series of cases. In 25 controls who received the usual antipertussis remedies the cough was frequent and rackin_g, and the course of the disease was long, varying from three to four months.

Postural Treatment—It is well known that the cough in pertussis is worse at night. In fact this has been accepted as one of the symptoms of pertussis. The reason for the incessant coughing at night has

Elixir Gold Tribromide (Elixir Bromaurate) may be obtained from Schieffelin & Co., New York City.

never been made clear. It occurred to me that this was due to an overstimulation, during sleep, of the cough center which is hypersensitive in pertussis. In the recumbent, sleeping position, the lungs do not expand fully and there is a decrease in oxygen and an increase in the carbon dioxide of the blood. This increased concentration of the carbon dioxide in the blood causes an over-activity of the hyperirritable cough center giving rise to the distressing paroxysms at night. To overcome this most annoying condition, I have whooping cough children sleep in a semi-reclining position. When propped up in bed, there is a better ventilation of the lungs with freer respiration, more oxygen inhalation, less carbon dioxide concentration and less stimulation of the cough center. This simple postural treatment is giving whooping cough children considerable rest at night.

SUMMARY

Whooping cough is a serious disease in its mortality rate, complications, and sequelae. It affects all races in all climates. It is essentially a disease of childhood. The etiology of pertussis is still not definitely established. The anatomic pathology shows an inflammation and degeneration of the upper respiratory tract. Physiologically, there is a hyperirritability of the coughing reflex arc which responds to the slightest physical or psychic stimuli. Most of the treatments recommended for whooping cough are either ineffectual or not practical of application. As a result of a study of many drugs, especially the bromides, in the treatment of whooping cough, gold tribromide is seemingly an effective remedy in a large number of cases. The earlier in the disease the treatment is begun, the quicker and better the results. The compound of gold tribromide inhibits the coughing reflex arc, allays the general nervous irritability and relieves the spasmodic attacks which cause damage to every system of the body.

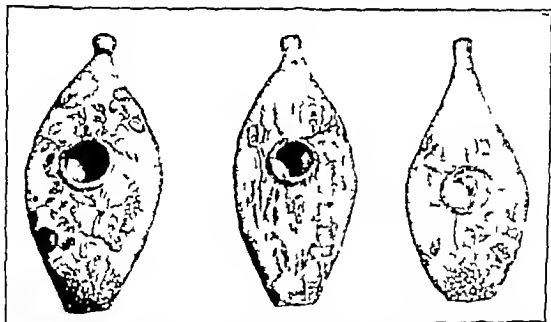
222 EAST EIGHTY SECOND STREET

ANTIQUES OF PEDIATRIC INTEREST

T G H DRAKE, M.B. F.R.C.P. (C)

AS EARLY as 1686 pottery works had been established in Staffordshire where clay and coal were easily obtainable

Josiah Spode the founder of the Spode firm was originally apprenticed to Thomas Whieldon, where he worked with Josiah Wedgwood. In 1770, he bought the pottery works of Banks and Turner at Stoke and in 1797 was succeeded by Josiah the second during whose period William Copeland was taken into the firm. Josiah the third died in 1829. In 1833 Thomas Garrett joined the firm and until his retirement in 1847 the firm was known as Copeland and Garrett late Spode.



Spode Staffordshire transfer printed pottery feeding bottles (length 7 inches)

Marks Left and right, Copeland and Garrett late Spode, circa 1833 center Copeland late Spode circa 1847

Since that time the style has been Copeland late Spode. The many productions associated with this famous factory are still perpetuated by Messrs W. T. Copeland and Sons.

In 1780, Thomas Minton engraved his famous willow pattern, evolving and arranging his design from several different Chinese sources. Originally there were only two figures on the bridge, no flying doves and no conventionalized cedar. The pattern was an immediate success. Different versions were engraved with additions from other Chinese originals and finally the pattern as we now know it was evolved. From the final composition has grown up the legend of

From the Department of Pediatrics, University of Toronto, and the Hospital for Sick Children, Toronto.

the love of a daughter of a Chinese mandarin for her father's secretary and the punishment by imprisonment of the daughter by her father who had intended her for an old but wealthy suitor, of the escape of the lovers to the cottage by the sea where the life honeymoon was to be spent, the burning of the cottage by the disappointed suitor and the transformation of the lovers by the Immortal Gods into two doves

Transfer printing of pottery was introduced into Staffordshire by Josiah Spode in 1784 with the old willow pattern. Later other blue printed designs were used.

Transfer printing is a method of printing on a rigid or uneven surface by means of paper prints applied to the ware. It was probably used first by the Battersea Enamel Works about 1750. Some what later its use in decorating pottery was discovered independently by Sadler of Liverpool who with Green was so successful in this method of decoration that pottery was sent to them from all parts of the country for printing.

In transfer printing a metal plate, usually copper, is engraved in the usual way but somewhat deeper than for printing on paper since the firing of the pottery reduces the strength of the colors. The color is then rubbed into the lines of the warmed plate the superfluous pigment is scraped off and the surface is wiped clean with a pad. A print is taken on dampened tissue paper and this is applied to the ware and carefully rubbed into contact. The piece is next immersed in water, which removes the paper and leaves the print unharmed since the pigment is mixed with linseed oil. The piece is then fired over or underglazed as the case may be.

Critical Review

TUBERCULOSIS IN CHILDREN

LEE FORREST HILL, M.D. DES MOINES, IOWA

IN THIS Critical Review of the October 1932 issue of THE JOURNAL OF PEDIATRICS, the attempt was made to sum up the prevailing views on tuberculosis in children. This discussion is intended as a continuation of that report and is based on the literature of the past year.

The National Tuberculosis Association¹ has published a second brochure entitled *Childhood Type of Tuberculosis Diagnostic Aids*, with chapters by Opie, Aronson, McIlhenny, and Chadwick. It has received the approval of the Committee on Childhood Tuberculosis of the American Sanatorium Association and is to be highly recommended to those who wish a clear and concise presentation of the subject in condensed form.

Dr. J. A. Myers² has also published a second book called *The Child and the Tuberculosis Problem* which not only sums up in detail the present conceptions of the subject but also contains many advanced ideas which he has acquired as a result of his extensive studies at Lymanhurst during the past decade.

The set up at Lymanhurst has embodied an unusual opportunity for a follow up study of a large number of tuberculous children over a period of ten years. The results of this ten year period of study have been published by Dr. Myers, chief of staff and by Dr. Chester Stewart, pediatrician on the staff in a number of articles. Their observations have forced them to conclusions that in many instances are in direct conflict with beliefs generally held but which on the whole have tended to simplify and clarify the whole picture. In the pages that follow the opinions of these authors have been freely set forth for the purpose of bringing out fully these new concepts established by them.

TERMINOLOGY AND CLASSIFICATION

Some controversy exists in the literature as to the classification of the various types of lesions occurring in children as the result of first infection by the tubercle bacillus. The brochure referred to above states that "The childhood type of tuberculosis is the name adopted by the National Tuberculosis Association to describe the diffuse or circumscribed lesions in the lungs and associated tracheobronchial lymph nodes resulting from a first infection of the pulmonary tissue with the tubercle bacillus. It is recommended that this term 'childhood type of tuberculosis' be used instead of 'infantile', 'juvenile' or 'hilum tuberculosis'. It specifically includes lesions of the tracheobronchial lymph nodes. The childhood type of tuberculosis is usually found in children. It infrequently occurs in white adults but is not uncommon in adult negroes, Mexicans, American Indians, Porto Ricans and Filipinos."

In a subsequent chapter McPhedran classifies the lesions of childhood type tuberculosis on the basis of x-ray observations as follows: "A Focal tuberculosis, caseous or calcied nodule B Tuberculous consolidation of a lobe or wedge, progressive or unstable, calcified spots remain if it clears C Tuberculous consolidation of a lobe or wedge, retrogressive and benign Few strands remain when it clears D Diffuse, childhood type tuberculous infiltration Confluent bronchopneumonia is the serious lesion of this type and often precedes E E Miliary tuberculosis F Tuberculosis of tracheobronchial lymph nodes, uncalcified G Tuberculosis of tracheobronchial lymph nodes, calcified "

Myers³ states that their present classification consists of

1 Negative to tuberculosis In this group are placed those children who are negative to the tuberculin test when a full milligram of tuberculin has been administered intracutaneously, and who have no other abnormal findings due to tuberculosis

2 Primary tuberculous infection This group consists of those children who react positively to the tuberculin test but in whom no evidence of tuberculous disease can be obtained by x-ray, physical, or laboratory examinations

3 Childhood type of tuberculosis In this group the children react positively to the tuberculin test and in addition have some evidence, usually by x-ray, of the location of the focus or the foci The lesion may be represented by a shadow indicating an inflammatory process which is progressing, stationary, or receding, or it may be represented by shadows indicating deposits of calcium These lesions need not necessarily be in the chest When evidence of calcium deposits is found in lymph nodes anywhere, particularly in the cervical region or in the mesentery, the classification is that of childhood or first infection type of tuberculosis Further subdivided into

(a) Those with the inflammatory stage when first seen, progressing, stationary or receding

(b) Consists of those lesions in which deposits of calcium can be demonstrated by x-ray examination

4 Adult type of tuberculosis In this group have been placed all of the definite clinical forms of tuberculosis whether the lesions appear in the lungs, bony framework, or elsewhere

Myers expresses dissatisfaction with his second group He feels that a sharp line should not divide cases with demonstrable lesions from those without demonstrable lesions when a positive tuberculin test is present in both groups He believes it is erroneous to attempt to distinguish between tuberculous infection and tuberculous disease A positive tuberculin test means a focus of tuberculous disease somewhere within the body, and only the pathologist has the right to say whether it is "healed" or not

Stewart⁴ in a more recent article expresses his belief that the terminology and classification set forth in the previously mentioned brochure should be revised in order that it be more in keeping with the known facts concerning first infection with the tubercle bacillus The term "childhood type tuberculosis" as now defined limits itself to include lesions occurring only in the lungs and tracheobronchial lymph nodes Since the primary focus or foci of infection may be extrapulmonary, and since the childhood type of tuberculosis does occur

in adults, Stewart feels that the terms "first infection types of tuberculosis" or "primary tuberculosis" would be more appropriate. Furthermore he objects to the term 'adult tuberculosis' on the basis that this lesion does occur in children with appreciable frequency. He prefers that these lesions be designated by the term 'reinfection type of pulmonary tuberculosis'.

He is not satisfied with a classification based upon appearance of lesions in the x ray films of chests. Compared to the tuberculin test and pathologic examination the x ray is a relatively crude screen since in only about 25 per cent of first infection cases does the x ray reveal lesions with sufficient clearness to be identified as such. Ghon⁶ in his well known pathologic studies was able to demonstrate a tuberculous focus in 90 to 95 per cent of positive tuberculin reactors. Both Stewart and Myers express their conviction that a positive tuberculin test specifically indicates a tuberculous focus somewhere within the body, but our present methods of examination during life are inadequate to demonstrate such foci in at least half the children.

Stewart further states that no evidence is found in the following observations made during the past decade at Lymanhurst to indicate that cases presenting single or multiple large, partially or heavily calcified scars show a definitely greater tendency to manifest symptoms of impairment in health referable to primary tuberculosis or to suffer a different ultimate fate than do infected children who have small or no lesions demonstrable during life. As far as I have been able to ascertain, all cases of primary tuberculosis are basically identical except that a few cases (from 3 to 4 per cent of infected children) with acute diffuse primary tuberculous pulmonary infiltrations exhibit symptoms which on this basis temporarily distinguish them for a time from the general group of infected cases. After these acute manifestations subside patients with first infection types of tuberculosis are clinically indistinguishable from one another as a rule and remain so until the day arrives when reinfections transfer a certain percentage of them to the consumptive group."

A classification proposed by Stewart outlines roughly the stages of evolution of tuberculosis as it occurs in man. The first group constitutes the general population. A second noninfected group is identified by negative tuberculin reactions. The third group is the primary tuberculosis group or first infection types of tuberculosis or 'patients whose bodies harbor foci of tuberculosis of first infection (identified by positive tuberculin reaction) [This group includes 'first infection pulmonary (childhood type by definition in the brochures) retroperitoneal or cervical lymph node tuberculosis]'. Note may be made in these cases relative to the appearance of lesions found but assumptions that visualized conditions provide reliable evidence that these cases differ basically and require grouping separate from others in the general first infection group apparently are unwarranted'. The fourth group contains first infection types of tuberculosis with symptoms. Only 3 or 4 per cent of infected children are in this group and their sojourn here is temporary. The fifth group is comprised of first infection types of tuberculosis without symptoms definitely referable to their disease. The majority of cases fall in this group. The sixth group is designated as the secondary tuberculosis group or first infection types that later develop reinfection types of tuberculosis (consumption, and the like). The final group is the primary tubercu

losis group or first infection types of tuberculosis that do not develop reinfection types of tuberculosis

Washburn⁶ feels that on the basis of newer knowledge secured by tuberculin, x-ray, and pathologic studies the terms the "pretuberculous" or "potentially" tuberculous child, "latent" or "suspected" tuberculosis are of doubtful value as diagnoses. The attempt to distinguish between "tuberculous infection" and tuberculosis he thinks is also of dubious significance, and the term "tuberculosis of childhood type" may be misleading. He prefers the classification as proposed by Ranke⁷ in 1916 in which the disease process is divided into three stages, a primary phase of invasion, a secondary phase of spread to lymph nodes associated with the development of an allergic response, and a tertiary phase which represents actual visceral involvement. The first two stages commonly occur in childhood and the third in adult life, but all three may be found in infancy. This is essentially the view of the German School as set forth in the *Handbuch der Kindertuberkulose* for 1930 by Herbert Koch, Epstein, Engle, Priesel, Zarß, Liebermeister, Weise, and others as referred to by Collis and Brookington.⁸

Blau and Rosenbaum⁹ feel it is a misnomer to designate the primary complex of Ranke as childhood tuberculosis. This latter term "should be limited to cases in which a definite and distinct parenchymatous involvement is depicted by the x-ray, with a positive Mantoux test, and with more or less distinct clinical manifestations, simulating in a measure pulmonary tuberculosis in the adult." They feel the pulmonary tracheobronchial gland lesions defined in the brochure as childhood type tuberculosis should be designated by the term "primary pulmonary tuberculous complex."

It is apparent, therefore, that there is still lacking by a wide margin a uniform opinion in the interpretation, terminology, and classification of lesions produced in the human body by the initial infection with tubercle bacilli.

LESIONS

From studies such as those which have been carried on at Lumanhurst and elsewhere, sufficient data have been collected to give the physician some idea of what he may expect in the way of x-ray findings in his positive tuberculin reacting children. Roughly speaking at least half of the positive reactors will have negative films, 25 per cent will show questionable or doubtful lesions, and the remaining 25 per cent will show definite lesions characteristic of the childhood type of tuberculosis.

In the 50 or more per cent of positive reactors who give negative roentgenologic findings the primary focus may be assumed to be extrapulmonary, too small to cast a shadow, or obscured by other structures. Except for this difference of visualization, or failure of visualization of lesions it probably should be emphasized that symptomless positive reacting children are in all essential respects to be regarded alike so far as their tuberculous experience is concerned.

In the 25 per cent of films revealing definite lesions, it may be expected that the parenchymal lesions will be found more often in infancy and early childhood, the calcifications in middle and late childhood, and the adult type of tuberculosis in the teen age.

Myers⁸ reports his x ray findings in 4737 positive tuberculin reactors as follows: Questionable calcification in hilum 4.12 per cent, slight, moderate, and marked calcification in hilum 9.35 per cent, Ghon tubercles 6.04 per cent, questionable Ghon tubercles 0.8 per cent, calcification hilum fibrosis extending into lung parenchyma 0.55 per cent, childhood type tuberculosis in lung parenchyma (inflammatory stage), 0.87 per cent, marked enlargement hilum, without calcification 0.38 per cent, marked enlargement hilum infiltration extending to parenchyma 0.8 per cent, total positive findings 22.91 per cent, adult type tuberculosis 1.28 per cent.

Stewart¹⁰ in a group of 579 positive reactors found the following lesions revealed by the x ray: Resolving parenchymal (comparable to childhood type tuberculosis in lung parenchyma (inflammatory stage) of Myers), 4.7 per cent, questionable calcification 8.6 per cent, slight calcification 13.8 per cent, moderate calcification 5.2 per cent, marked calcification, 2.2 per cent, Ghon tubercles, 11.6 per cent, adult type tuberculosis 2.2 per cent.

RESOLVING PULMONARY LESIONS

Some further discussion of the lesion referred to above by Myers as the childhood type tuberculosis in lung parenchyma (inflammatory stage), and by Stewart as resolving parenchymal pulmonary tuberculosis seems warranted. It is probable that this is the same lesion referred to by Eliasberg and Neuland, Goldberg and Gasul and others, as "epituberculosis" and in all probability in the past the terms "aplenopneumonia," "gelatinous pneumonia," "perifocal inflammation," "circumfocal inflammation," "paratuberculosis," "perituberculous inflammation," and "collateral inflammatory edema" were all used to designate this same type of lesion. In common with all descriptions, has been the basic fact of a more or less massive slowly resolving pulmonary shadow, characterized by paucity of physical signs and symptoms occurring in children who have positive tuberculin reactions. According to Stewart¹⁰ such lesions represent the earliest stage of the primary pulmonary infection. Up to date he has observed seventy-three such cases. Two of these have been under observation for nine months, a third for twenty-eight months, and the remaining sixty-eight cases for periods ranging from three to nine years. No deaths have occurred. He states that "In most cases (all in our experience) extensive parenchymal lesions resolve and disappear leaving relatively inconspicuous calcified scars and, during the months this resolution is taking place the patient, whether a young infant or an older child, may enjoy excellent health. At times severe and alarming symptoms are present for variable periods early in the course of the disease, following which a long period of symptomless convalescence ensues."

Martin¹¹ in California presents a series of sixty cases that she has seen. She divides them into three groups on the basis of variation in physical signs and symptoms rather than on any fundamental pathologic differences. All the children had positive tuberculin tests. Sixty-five per cent had a history of contact. Eighty per cent of the children were under six years of age. All had pulmonary infiltrations of varying degrees of massiveness as revealed by the x ray. Twenty-nine were acutely ill with physical signs of consolidation. Eighteen of the sixty were ailing but had slight or absent physical findings. Thirteen were apparently healthy children with practically negative symptoms.

and physical findings Four of the series died Three of these were in the acutely ill group and were seriously ill when first seen, the other death, due to tuberculous meningitis, was in the second group In the remainder, the parenchymal lesion gradually resolved leaving either an area of calcification or cleared completely Atelectasis of a lobe was present in three cases Evidence of enlarged tracheobronchial lymph nodes in association with the pulmonary infiltrations was present in 45 per cent of the series Martin does not feel the presence of these enlarged glands added greatly to the gravity of the prognosis She concludes that "acute tuberculous pneumonias are more frequent than is generally recognized They have a good prognosis if seen early, and if repeated infection is prevented by separation of the child from the source of infection "

Bruce¹² also discusses this lesion and the favorable prognosis of primary tuberculosis in general, and presents films of four cases of pulmonary tuberculosis which he has seen undergo satisfactory resolution

Reichle,¹³ in a most interesting article, discusses the mechanism of resolving exudates in tuberculous children He regards the observations of the authors who first called attention to these massive lobar shadows as being of crucial importance However, he believes that up to the present time there is no unanimity of opinion concerning the nature of such lesions Atelectasis, secondary pyogenic infection in tuberculous tissue, and lymphatic congestion have been suggested as mechanisms The majority, however, look upon these exudates as being areas of inflammation about tuberculous tissue, the inflammation being due to a "poison" from the destroyed tissue or a "toxin from the tubercle bacillus in the focus of 'true' tuberculous inflammation " The rôle played by allergy in the production of these resolving or "fugitive" exudates is discussed by the author He states that "allergy is probably an essential condition of a fugitive exudate " To quote further, "The primary infection occurs in virgin soil, the tissue is not specifically sensitized to the tubercle bacillus and its chemical constituents This is probably the reason for the minuteness of the lesion, the slight surrounding inflammation, and the ultimate state of characteristic morphology Never again can the body react to the tubercle bacillus in this fashion, every subsequent defense will be conducted with a striking increase in the auxiliary phenomena of peripheral vascular dilation and extravasation of the cellular and amorphous material which constitutes an inflammatory exudate The second characteristic of hypersensitive tissue is its tendency to undergo the type of necrosis known as caseation " He feels that the majority of the lesions under discussion are tuberculous pneumonias which have failed to go on to caseation, some may be atelectases, and some lobar or bronchopneumonias He disagrees with Stewart's idea that these resolving lesions are restricted to the stage of the primary infection He concludes that "since resolution is possible in almost every form of tuberculous inflammation, there is no reason for calling on any unusual mechanism to explain the retrogressive tuberculous exudates "

H C Cameron¹⁴ describes a case of apparent resolving parenchymal tuberculosis which cleared rapidly leaving a small focus He concludes "that the existence of benign infiltration remains to be proved It can only be demonstrated by the accident of an opportunity being afforded to perform an autopsy during the time when the extensive consolidation is present "

Whether the lesion which has been referred to by such a galaxy of terms has some unusual pathogenesis uncommon in tuberculosis knowledge, or whether, as Stewart suggests, it merely represents the usual course of events in primary infections is probably still an open question. However, the increasing frequency with which resolving lesions are being reported coincident with the increasing use of tuberculin and x ray suggests that in the past they have gone unrecognized, and to this extent lend support to Stewart's idea.

IMMUNITY

Perhaps one of the most revolutionary ideas that has developed as a result of the study of tuberculosis in large numbers of children by means of tuberculin and x ray is that a primary infection does not confer protection against phthisis. In other words, a positive tuberculin test in a child can no longer be held to be an advantage, as an indicator of immunity. Nor can it be held to be a liability to reach adult age with a negative test. Myers³ has observed nurses on tuberculosis wards, who, at the beginning of their services reacted negatively to tuberculin but who later developed positive tests. X ray pictures of their chests have shown lesions similar to the primary type of infection seen in children. In no instance has he seen "galloping consumption" occur in adults who had grown up with a negative test as was once supposed to be the fate in store for such unfortunates if they chanced to acquire tuberculosis.

If our former ideas are correct, one would not expect to see adult type tuberculosis developing in healthy children with positive tuberculin tests showing evidences of primary tuberculosis only. Stewart,⁴ however, in reporting his observations on 10,000 children at Lymanhurst in the last ten years found eighty-four cases of phthisis, thirty-six of whom had had primary tuberculosis exclusively for varying periods up to ten years and then developed the reinfection type of pulmonary tuberculosis. Twenty-five of the eighty-four children had primary and reinfection pulmonary tuberculosis coexisting when first examined. Thus sixty-one or 73 per cent of these eighty-four children with phthisis presented unmistakable evidence that their primary infections did not prevent them from developing the serious and fatal form of adult or reinfection type tuberculosis. Insufficient data were available on the remaining twenty-three children to provide evidence for or against the question under discussion. Opie at the autopsy table found lesions of primary tuberculosis in all cases of reinfection type or adult type of tuberculosis. It would seem, therefore, on the basis of such evidence as presented above that the allergic state does not imply protection, and the necessity of preventing continued exposure to tubercle bacilli whether it be the infant with his primary infection just beginning, or the older child with his calcification well established far overshadows all other considerations combined in the treatment and prevention of tuberculosis in children.

PROGNOSIS

The opportunity of watching a comparatively large number of primary pulmonary infiltrations resolve and finally end in the production of Gohn tubercles or other calcifications has led Stewart¹⁵ to the belief that infants and children seldom, if ever, succumb to a single primary infection. He believes an individual can resolve a primary infection

to the calcified stage once and only once. In no instance has he observed a subsequent repetition of this process in the same child, nor has he observed a case of phthisis which has developed as a direct result of a first infection. Repeated reinfections may, of course, overcome the natural powers of resistance of the child and result in fatal generalized or reinfection types of tuberculosis. In the days before the use of tuberculin and serial x-ray films, it was only cases of this latter type that were recognized and the natural assumption was that tuberculosis in early life was an extremely serious disease. That such an outcome, however, is the exception rather than the rule, and that children are endowed to cope with reasonable doses of tubercle bacilli on the whole equally well, if not better than adults, is one of the remarkable changes in thought being brought about by these newer methods of study. The almost universal good health found in the group of children with primary infections, the majority of whom are unaware of their tuberculosis, or when it started, has led to the logical conclusion that first infection type of tuberculosis is a benign form of the disease, in contrast to reinfection types which are progressive and tend to be fatal.

TREATMENT

Both Myers⁸ and Stewart¹⁶ have pointed out the conclusions they have reached in regard to the treatment of primary tuberculosis. The one essential is that opportunity for reinfections must be prevented. For this reason, and because of the uniformly favorable outlook in this type of the disease, they believe sanatorium care, even with massive resolving pulmonary lesions, is undesirable and unnecessary. Well managed homes, or foster homes free from tuberculosis, provide all that is necessary in the treatment of such patients without adding the risk of reinfection, which is a possibility in the hospital ward or sanatorium.

Children who develop the adult type of tuberculosis need sanatorium care. Myers⁸ agrees with Chadwick that collapse therapy for these cases is indicated much more frequently than has been the custom in the past.

EVOLUTION OF TUBERCULOSIS

By way of summary of what has been said heretofore, the following outline, representing Stewart's¹⁰ conception of the evolution of tuberculosis in the human lung, is presented.

- 1 Primary tuberculous infections of the lungs are revealed by the roentgen ray films as parenchymal infiltrations, calcified glands, and Ghon tubercles.

- 2 These lesions, although varied in appearance, merely represent different stages in the development of one and the same clinical condition, namely, primary tuberculosis, or tuberculosis of the childhood type.

- 3 The general tendency for lesions resulting from an initial infection by the tubercle bacillus is first to resolve and later to calcify.

- 4 The human body can resolve a tuberculous infection into what is known as the primary complex only once.

- 5 When once reduced to calcified scars, these primary tuberculous lesions do not become reactivated later in the production of the adult type of tuberculosis (consumption).

6 Death seldom and possibly never results from a single primary pulmonary tuberculous infection. The prognosis is excellent in infancy as well as in later childhood provided reinfection is prevented.

7 Primary tuberculous infections of the lung if extensive produce symptoms of varying severity which subside in the course of a few to several weeks. Thereafter throughout the remainder of the life of the patient these primary lesions produce no clinical symptoms. (Occasionally a very large Ghon tubercle acting as a foreign body may erode a blood vessel and cause hemoptysis and in rare instances may be expelled from the lung in coughing.)

8 Consumption (phthisis) does not develop as a result of an initial infection by the tubercle bacillus. The first infection occurring at any age in life uniformly resolves and calcifies.

9 Consumption develops following a reinfection of individuals who previously have had a primary infection.

10 The reinfections responsible for the development of phthisis are probably exogenous in origin in the majority of cases.

11 The lesions of reinfection (adult type of tuberculosis or phthisis) usually appear in the subapical portions of the lungs.

12 These lesions may be present for months and years without producing symptoms, physical findings or showing any tendency to spread.

13 During the years previously dormant lesions characteristic of the adult type of tuberculosis frequently tend to spread, produce cavities and cause death.

14 The adult type of tuberculosis seldom calcifies.

15 Puberty seems to favor the breaking down of previously existing apparently quiescent subapical infiltrations of the adult type of tuberculosis. Primary infections occurring during puberty however behave much the same as similar infections taking place in infancy and early childhood.

16 Lesions of the adult type of tuberculosis tend to spread and cavitate whereas infiltrations resulting from initial tuberculous infections tend to recede and calcify.

17 The prognosis is grave for the adult type of tuberculosis. This type of the disease frequently results in death whereas primary infections are seldom fatal.

18 The relationship existing between the childhood and the adult type of tuberculosis seems to consist largely in the tendency for the primary infection to prepare the patient for the development of phthisis should he perchance later experience a reinfection of sufficient severity to produce an intrapulmonary lesion.

19 Phthisis apparently does not ordinarily result from a lighting up of an old infection received in childhood.

20 The part the former childhood infection seems to play in favoring the later development of phthisis depends more upon the changes which this primary infection caused with respect to the manner in which the body reacts thereafter to the tubercle bacillus and its products rather than upon a lighting up of the old disease acquired during childhood.

MODERN CASE FINDING

One of the most important recent developments in the public health phase of tuberculosis work is area testing, or case finding. The object is to search out the spreaders of tubercle bacilli and find infected children before they have developed serious tuberculous disease. Proper disposition of these two groups is, of course, the final goal.

The success achieved by the veterinarians in stamping out the disease among cattle is an example and a challenge to the workers among human beings. "In certain parts of the United States," says Stewart,¹⁷ "certified areas exist in which no cow is in danger of contracting tuberculosis from other members of the herd, and in these certified districts to be a calf is safer than to be a baby, in so far as tuberculous infection is concerned." And again Myers² remarks that some herds of cattle are in greater danger from human sources of tuberculous infection than from bovine sources.

So long as the opinion was held that tuberculosis was practically universal after the age of ten, tuberculin testing had a very limited field of usefulness, but when area testing of children showed a variation of positive reactors from 10 per cent in some rural communities, to as high as 75 per cent in certain sections of large cities, with an average among large groups of children of around 28 per cent, the possibilities of a tremendously increased field of usefulness of diagnostic tuberculin in screening out the infected from the uninfected became apparent.

The x-ray, too, must be given its full share of credit for the new vista which has opened up in the control of the great "white plague." An x-ray film of every positive reactor is now considered an essential. Amberson, Barnard, and Loew¹⁸ conducted an experiment with paper films and conclude that while they are not quite as clear as celluloid films, they are satisfactory for most diagnostic work, and that the disadvantage is offset by the greatly increased number of films that may be taken with no increase in expense.

Also, the clearer realization that as a contagious disease, tuberculosis presents an epidemiologic problem not dissimilar in many respects to that of typhoid fever or diphtheria, has brought out the possibilities of public health regulations for the control of this disease that may in time be equally effective with those in force for the control of other contagious diseases. It is interesting to note that Geer¹⁹ has instituted a medical aseptic technic in the tuberculosis division of the Ancker Hospital in St. Paul. From 1928-1930 an incidence of tuberculous disease of 55 per cent developed among the nurses of the training school. From 1931, when the new technic went into effect, up to the present time, the incidence of tuberculous disease has been only 16 per cent, which compares favorably with that found among the nurses of five other general hospitals.

How long it will take for area testing of children to become as general over the country as testing of cattle now is can only be surmised. Already many states have begun in earnest to attack the problem. Massachusetts with its ten-year program, and 100,000 children tested in the first five years, is the outstanding example. Tennessee, as reported by Bishop and Stewart,²⁰ five years ago embarked on a state wide program for control of tuberculosis with "the central and dominating idea behind this program to bring about finding of every case of tuberculosis as early as possible and placing all

cases found under adequate medical and nursing care " They conclude that " The logical means of approach in the control of tuberculosis in Tennessee, in the light of information now at hand, would seem to center around the breaking of the chain of long-continued contact between patients with fibroid and other types of tuberculosis with their household associates Eventually this would mean the establishment of hospitals or retreats for the care of the patient who is spreading tuberculous infection among members of the family and friends "

In Minnesota, Anderson²¹ reports the results of tuberculin testing surveys carried on by ten county tuberculosis sanatoria These ten institutions tested a total of 23 424 children of whom 16 76 per cent were positive, 89 16 per cent of the positive reactors were x rayed, 10 per cent showed evidence of childhood tuberculosis and 2 per cent adult tuberculosis "The goal of these sanatoria " says Anderson, "is year by year to come closer to an accredited group of school children "

Surveys have been carried on in Delaware by Phillips,²² and by Sargent²³, in Texas by Gray²⁴ and by Sellers²⁵ in Colorado by Einhorn²⁶ and in Yonkers New York by Littell²⁷ Brachman²⁸ gives the results of case finding in three high schools in Detroit He says that "The Detroit Tuberculosis Society's custom, of giving health certificates to high school graduates on physical examination, will in the future include tuberculin testing and x raying of the reactors "

Leggett and Myers²⁹ studied the incidence of tuberculous infection among the high school students of Morrison County, Minn Three hundred seventy six tests were made with 14 9 per cent positive reactions

Hewitt and Cutts³⁰ tested 1328 high school students in Rochester, Minn, and found 11 5 per cent reacting positively Of thirty four students definitely known to have been exposed to open tuberculosis 61 8 per cent were positive 15 1 per cent of the positive reactors had x ray lesions suggestive of tuberculous infection

Soper and Wilson³¹ made stereoscopic films of all the entering classes (1 644 entrants) at Yale University in 1930 and found thirty, or 1 8 per cent, showed evidence of pulmonary tuberculosis and 229 or 14 4 per cent, showed calcifications designating the childhood type In 1931 tuberculin tests were made on the 1 502 entrants, 59 7 per cent gave a positive reaction The reactors were examined under the fluoroscope and any showing a suspicious shadow were x rayed Thirteen were found to have pulmonary tuberculosis From this study the authors conclude that fluoroscopy as a method is not sufficiently accurate The method to be used in 1932 will be a single film of all entering students They point out the superiority of routine roentgenography of students' chests in detecting tuberculosis over the method of physical examination alone used in the decade previous to the present study

Myers and Wulff³² gave their observations on tuberculosis in students at the University of Minnesota for the last eleven years Since 1928 tuberculin testing has been routine on all entering classes About one third of the students react positively The cost has prohibited x raying all the positive reactors but many have been done at the students' expense Since 1929, routine x raying of the entering classes to the School of Nursing and School of Medicine has been practiced Each year a new film has been made so that senior students will have been x rayed at least four times It is hoped to extend this service to

all classes in the near future. By this method it has been possible to determine almost exactly when infection has occurred in these two precarious professions, and to trace the source of infection with considerably less difficulty.

Prior to 1928, the method of finding cases of tuberculosis among the students was to wait for them to present themselves for examination because of illness. Several cases are cited to show the faults of this latter plan. Frequently the disease had progressed to such a far advanced stage when the diagnosis had been made on physical signs and symptoms that death or very serious illness was the inevitable result. Furthermore, such individuals were frequently spreaders of tubercle bacilli among their fellow students on the campus. In the future, it is the plan at the University of Minnesota to test all entering students with tuberculin, say the positive reactors, and repeat the testing on all negative reactors at intervals throughout the university course.

Other surveys have been reported, particularly among the Indians in the Midwest and Northwest, and among the Orientals, but perhaps the above citations are sufficient to show that a real beginning has been made with modern weapons in a direct attack upon the strongholds of tuberculous disease. It is certainly to be hoped that other states will realize the value of this splendid work, and embark upon programs that have as a goal the eradication of tuberculosis within their borders.

REFERENCES

- 1 Childhood Type of Tuberculosis. Diagnostic Aids. National Tuberculosis Assn 1931
- 2 Myers, J. A. The Child and the Tuberculosis Problem, 1932
- 3 Myers, J. A. Ten Years at the Lymanhurst School for Tuberculous Children. *Ann Int Med* 6: 672, November, 1932
- 4 Stewart, C. A. Does a Primary Tuberculosis Infection Afford Adequate Protection Against Consumption? *J A M A* 100: 1077, April 8, 1933
- 5 Ghon, Anton. Der primäre Lungenherd bei der Tuberkulose der Kinder, Berlin, Urban and Schwarzenberg, 1912
- 6 Washburn, Alfred H. Diagnosis and Course of Tuberculosis in Infancy and Childhood, *Nat'l Tub Assn*, 1932 pp 361-370
- 7 Ranke, K. F. Primary Lesion, Secondary and Tertiary Stages of Lung Tuberculosis, *Deutsches Arch f klin Med* 119: 1916
- 8 Collis, R. F., and Brockington, C. Fraser. Tuberculosis in Childhood, Its Etiology and Prognosis as Shown by the Stomach Lavage Method of Obtaining Tubercle Bacilli, *Lancet* 224: 127, Jan 21, 1933
- 9 Blau, A. I., and Rosenbaum, L. Childhood Tuberculosis—A Misnomer? *M J & Rec* 136: 19, July 6, 1932
- 10 Stewart, C. A. The Evolution of Tuberculosis in the Human Lung, *Am J M Sc* 184: 346, March, 1933
- 11 Martin, Ann. Tuberculous Pulmonary Infiltrations in Childhood, *Am J Dis Child* 44: 754, October, 1932
- 12 Bruce, J. W. The Prognosis of Tuberculosis in Infancy, *Trans Sect on Ped* 1932, p 209
- 13 Reichle, H. S. Resolving Exudates in Pulmonary Tuberculosis of Childhood. *Am J Dis Child* 45: 307, February, 1933
- 14 Cameron, H. C. On Fpntuberculosis. *Gov's Hospital Reports* 82: 290, October, 1932
- 15 Stewart, C. A. The Diagnosis and Clinical Characteristics of Pulmonary Tuberculosis in Children, *J Iowa M Soc* 22: 433, September, 1933
- 16 Stewart, C. A. The Prognosis and Treatment of Resolving Parenchymal Tuberculosis of First Infection in Infants and Children, *Am Rev Tuberc* 24: 597, November, 1932
- 17 Stewart, C. A. The Child's Bill of Rights in Relation to Tuberculosis. What May the Child Expect? *Trans Nat'l Tuberc Assn* 1932, p 191

- 18 Amberson, J Burns Jr Burnard M W and Low M F Comparative Value of Paper and Celluloid Films for Roentgenograms of the Chest Trans Nat'l Tuberc Assn. 1932 p. 136
- 19 Geor E. K Primary Tuberculosis Among Nurses Trans Nat'l Tuberc. Assn., 1932 p 129
- 20 Bishop, E L. and Stewart H. C Tuberculosis in Tennessee, J. A. M. A 99 356, 1932
- 21 Anderson, A S The Value of Tuberculin Testing Surveys in Our County Tuberculosis Sanatoria Journal—Lancet 52 222 April 1, 1932.
- 22 Phillips, L. D Pulmonary Tuberculosis in Childhood Delaware State M J 4 183 August 1932.
- 23 Sargent, C. A A Report on Tuberculosis and Hookworm, Delaware State M J 4 181 August, 1932.
- 24 Gray G. A. A Health Survey of Abilene High School Students, Stressing the Incidence of Tuberculosis Texas State J M 28 269 August 1932
- 25 Sellers E. D The Evaluation of Tuberculin Tests and Chest Roentgenograms in a School Health Survey Texas State J Med. 28 212 August, 1932.
- 26 Euborn N. H Summary of Health of Children in Midwest Grade School, Colo Med. 29 141 March, 1932
- 27 Littell, E. G Early Diagnosis of Tuberculosis Among Children, Am. Jour Pub Health 23 146 February 1933
- 28 Brachman, D S Modern Case-Finding in Tuberculosis, Am. Rev Tuberc 24 89, July 1932
- 29 Leggett Ellis A., and Myers J. A The Incidence of Tuberculous Infection Among the High School Students of Morrison County Minnesota, Am Rev Tuberc. 26 559 November 1932
- 30 Hewitt Edith S and Cutts R. E. The Incidence of Tuberculous Infection Among Students of a High School Am Rev Tuberc. 25 525 April, 1932.
- 31 Soper, W. B and Wilson J. L. The Detection of Pulmonary Tuberculosis in 3000 Students Entering Yale University Am. Rev Tuberc. 26 548 November 1932
- 32 Myers J. A and Wolf Marjorie Eleven Years Observations on Tuberculosis Among University Students, Am. Rev Tuberc 28 339 November 1932

American Academy of Pediatrics

Proceedings

THIRD ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

MONDAY AFTERNOON SESSION

June 12, 1933

Round Table Conference on Rheumatic Heart Disease in Children

The meeting was called to order at 2 15 P M in the Berwyn Room of the Edge water Beach Hotel by the Chairman, Dr Hugh McCulloch, St Louis, Mo

DR HUGH McCULLOCH—This conference on rheumatic heart disease is to follow the one held last year under the direction of Dr Morse The general subject of rheumatic infection was covered by him and many important questions relating to diseases of the heart were presented In order to continue the discussion, it has been deemed wise to present four principal articles and to limit discussion to these I have therefore selected four separate articles, each of which is somewhat different and yet all are related

First A definition of what the rheumatic state or rheumatism means

An antigen (toxin) formed by recurring infection in one or more areas of the body (sore throat, common colds) and operating in an injured host (malnutrition) produces fixed (proliferative) and/or wandering (exudative) tissue response in the various susceptible parts of the body

- a. Tonsillitis/nasopharyngitis (sore throats, colds)
- b. Arthritis (joint pains)
- c. Carditis—myo, endo, peri (heart disease)
- d. Encephalitis (chorea)
- e. Nephritis
- f. Pneumonitis
- g. Peritonitis

The second article for discussion would be the factors which influence the manifestation of rheumatic fever and heart disease in children

- 1 Type of response shown by the patient
 - a Sensitized individual (exudative)
 - b Desensitized individual (proliferative, hyperplastic, aplastic)
 - c Nonsensitized individual
- 2 Age when the first attack occurs
 - a Progressive and recessive growth of tissue
- 3 Race.
- 4 Climate
- 5 Social status.

The third article is the care of children who have rheumatic heart disease

- 1 During the period of active infection.
 - a. Evidence of active focal infection fever rheumatic nodules
 - b. Treatment, clean out foci of infection Salicylates rest Congestive failure
- 2 During the period of convalescence
 - a. When does it begin? Normal temperature and pulse rate. Good appetite no fatigue
 - b. Criteria of satisfactory progress Gain in body weight and height to expected normal. Freedom from infection.
- 3 During the period of quiescence
 - a. Avoid infection by contact.
 - b. Daily routine balance of activity and rest.
 - c. School and/or work. Desirable Fitting for life work. Learn limitations.
 - d. General health. Food calories, variety vitamins, fluid. Sunlight, fresh air Quiet, sleep
- 4 The time when they become healed, or we think they are cured.
 - a. Prognosis Myocarditis. Endocarditis (aortic and mitral) Pericarditis.
 - b. Probable chance of recurrence

The fourth article is the discussion of the relation of rheumatic fever and heart disease in children to heart disease in adult life.

- 1 Healed juvenile types in adult life aortic and mitral chronic cardiac valvular disease
- 2 Subacute bacterial (streptococcus) endocarditis in old congenital or acquired heart disease
- 3 Myocardial failure after an old myocardial injury from rheumatic fever scarlet fever pneumonia influenza, diphtheria syphilis
- 4 Coronary heart disease.

The presentation of the first two subjects will be taken up followed by a discussion before proceeding with Articles 3 and 4

Definition of Rheumatic Infections—It is very apparent that 'rheumatic infections' is an inclusive term used to cover many manifestations of the rheumatic state in different individuals. For many years the term 'rheumatism' was used to define those conditions associated with painful swelling and structural changes in joints, as well as certain other symptoms and signs more or less related to the joints. Following this early use there occurred a period when an attempt was made to differentiate more clearly the various lesions occurring in rheumatism and there has been a tendency to differentiate these diseases too sharply and to do away with the older term. Since rheumatic infection in children is a process involving many parts of the body in different ways and at the same or at different times it may be advisable to again use a single term 'rheumatism' or 'rheumatic infection' or the 'rheumatic state' to include these various protean manifestations. Since heart disease is such a constant and important manifestation of rheumatism in children it may be advisable also to include 'rheumatic heart disease' as a general term of the same sort as the others. The decision as to which term is best will probably rest with common usage and not come about by any special edict or order.

The following definition of the rheumatic state is now proposed for discussion.

An antigen (toxin) formed by recurring infection in one or more areas of the body (sore throat and common colds) and operating in an injured host (malnutrition) produces fixed (proliferative) and/or wandering (exudative) tissue response in various susceptible parts of the body."

The nature of the antigen producing the changes in the body is not yet certain. Investigative work done so far indicates that this substance is not of the nature of a filtrable virus, though this possibility cannot be finally dismissed. Recent studies on the virus of the "common cold" reported by Dochez may have some bearing on a virus of a similar sort being the antigen of rheumatic fever. The experimental evidence suggests that it is a bacterial product of the general order of toxins formed by streptococci growing in some focus, usually in the nose and throat area. Specificity for either the toxin itself formed by the organisms or for the organisms themselves has not been proved. Indeed, the more recent bacteriologic studies of Swift and others seem to indicate that many organisms may be responsible at times, or that one organism may liberate different toxins at times.

The nature of the infection which liberates the antigen varies a great deal, it may be a single infection in the tonsils or recurring infections of varying severity in the nose and throat area, or it may be located in other parts of the body. The tonsils, the nasopharyngeal mucous membrane and the sinuses, however, seem to be the usual areas involved. This infection may manifest itself in different ways, either as sore throats, common colds, coryzas and tonsillitis.

Malnutrition must play an important part in determining the incidence of rheumatic infections as well as their manifestations in a given child. Malnutrition manifests itself in children in many ways, all of which are more or less familiar to us and need not be discussed fully at the present time. It has been our observation in a large group of cardiac children that most of them give a history during infancy and childhood of improper feeding, housing, general care, and of recurring infections of the type usually considered to be associated with a low body resistance and malnutrition. How important this association may be is difficult to prove. Its high incidence, however, suggests a probable close relationship. The usual conception of malnutrition in children is that of underweight and undernutrition with a low body resistance to infection. It should be pointed out, however, that quite frequently children may be obese and suffer equally from malnutrition and low body resistance to infection. We have observed this type of malnutrition very frequently in children with chorea.

The nature of the manifestations of the rheumatic state in children varies, and may be of two general types. First, a response on the part of the fixed tissue elements of the body, producing structural changes in the various parts of the body, particularly the heart. These have been classified by Swift as proliferative changes. The essential process is the formation of rheumatic nodules (Aschoff bodies), together with changes in the heart muscle, in the valves and the pericardium. These lesions occur also in other parts of the body, particularly in the brain and lungs. The second type of response is due to changes in the wandering tissue elements of the body, characterized principally by acute transient exudative processes such as leucocytosis, fever, edema, etc., in joints, heart structure, brain or skin. While these two types can be well defined and frequently children may be seen who belong entirely to one or the other type, there may be children who show signs belonging to both types who, therefore, are mixed. The exact clinical differentiation at times, therefore, may be difficult.

While manifestations of the rheumatic state occur in many parts of the body, there are certain principal locations where it is usual to find either or both, proliferative and exudative changes.

a. The tonsillitis and/or nasopharyngitis is regarded as the initiating cause of an attack of rheumatic fever and serves as the focus of infection from which the antigen is liberated. It also seems probable that the inflammatory changes in the tonsils and/or nasopharynx may be a manifestation of the rheumatism itself. Full

discussion and investigation is very much in order on this point. It may be pointed out that a child who suffers from rheumatism should be seen by the attending physician during the time when the acute process in the nose and throat area is going on in order to determine the appearance of the lesion then as well as in the interim between attacks. It is only in this way that a proper classification of this process can be made.

b Painful joints are a common manifestation of rheumatism from which the condition derives its important terminology. When true joint pains occur in children they are usually due to rheumatism and except for the occasional small child who has a "septic arthritis rheumatism should be suspected in all who complain of joint pains. Opinion today definitely excludes growing pains as a manifestation of rheumatism indeed, there should be serious question as to whether pain can result from growth in any way. Its further use should be discouraged. The most important pain in the extremities occurring in children not due to rheumatism is that which results from fatigue. In our opinion, this type of pain is very common and simulates closely that of rheumatism. It usually occurs at night after going to bed, is usually in the lower extremities and is not associated with other signs of rheumatism. It is described by the child as a soreness in the legs and does not occur in the region of the joints. In such children flat feet must be considered also.

c The manifestations of rheumatism in the heart are so well known that they need not be discussed here. Suffice it to say the three important regions of the heart are usually involved and in a child who has repeated attacks of rheumatic fever one may safely assume that the endocardium and the myocardium are always involved, and that sooner or later the pericardium will show changes. The term carditis is used frequently by pediatricians to indicate the widespread changes occurring in the hearts of these children. Endocarditis should mean rheumatic heart disease with endocarditis.

d Chorea is frequently found in connection with rheumatic manifestations and more and more is being looked on as a specific type of encephalitis due to the action of the toxin in the brain, particularly in the lower basal nuclei. These changes in the brain usually are of the exudative type though occasionally rheumatic nodules and proliferative changes may be found.

e The relationship between inflammatory changes in the kidney due to infection and rheumatism is not so clear. It has been our observation that children with rheumatic heart disease show some form of nephritis more frequently than a normal group and it also is well known that children with nephritis resulting from infection in the nose and throat frequently may have important structural changes in the heart. When these changes occur they are of the type usually found in acute rheumatic fever. The relationship may not be close but there are certainly many similar points. Children with nephritis do not show rheumatic nodules in the kidney tissue though the crescent changes in the glomeruli may at times simulate this same process.

f In the last ten years pathologists have pointed out lesions in the lungs and pleura which probably are of a rheumatic nature. Structures resembling Aschoff bodies have been found and the interstitial change in the lungs and pleura bears many resemblances to the lesions in the heart muscle and endocardium. Von Glahn and Pappenheimer have pointed out the probability that pneumonitis and pleuritis of this type may be a manifestation of rheumatic fever.

g Certain cases of peritonitis have been reported in which it seems probable that the lesion was due to rheumatism. These case reports so far have not been frequent though it is quite possible that many of them have either been overlooked or have not been investigated with the idea of a possible relation to rheumatic infection. This point can be carefully investigated when suspicious cases occur.

Factors Influencing the Incidence and Manifestation of Rheumatic Fever and Heart Disease in Children

1 It has been pointed out by Swift that the nature of the rheumatic infection varies with the type of response shown by the patient to the infection. In individuals who have been sensitized previously to streptococcal infection, particularly adults, an attack of rheumatic fever manifests itself principally by exudative signs, especially painful joints, with redness and swelling, fever, leucocytosis, prostration, and by acute myocarditis, endocarditis and pericarditis. It is also known that such an individual tends to show well defined attacks of rheumatic fever with a period relatively free from activity in between. These cyclic attacks are not seen commonly in children. It also has been shown that individuals who have been sensitized to streptococcal infection, probably will show proliferative changes of a hyperplastic type, especially rheumatic nodules, Aschoff bodies, chronic or subacute myocardial, pericardial and endocardial changes and pneumonitis. This type of response can be reproduced satisfactorily in laboratory animals. In the non sensitized individual, the proliferative response is usually aplastic in nature and not associated with the formation of rheumatic nodules and Aschoff bodies, but with a progressive injury described by Swift as a "cachectic" or "anergic" type. It is this type which we have seen frequently in very young children during the first attack of rheumatic fever, and with a fatal termination.

2 The age of the patient when the first attack of rheumatism occurs apparently determines to a considerable extent the manifestations of rheumatic fever. During childhood the process is apt to be widespread throughout the body as well as involving all parts of the heart. It also is during this period that the joint pains are less severe and less constant and in early childhood, particularly under the age of two, joint pains rarely occur. During adult life the joint pains occupy a much more prominent part of the picture of rheumatism and the disease is more localized in any tissue. It is also well known that the chance for the heart to be involved during adult life is much less than during childhood. It is interesting to note that certain adults may show the same form of rheumatism seen during childhood. It is probable that these individuals have never had an attack of rheumatic fever or an infection of this type previous to the onset of the disease. We have had opportunity to observe on several occasions, children who have shown attacks of rheumatic fever similar to that seen more frequently during adult life. These children in each instance have shown other signs of biological maturity and growth, so as to make it seem probable that the nature of their rheumatic attack was determined by an early maturity. This difference in age periods needs further study and clarification. It is suggested that the important subject of the nature of growth may determine itself the type of response shown by the patient. It is quite possible that during the period when progressive growth is taking place, i.e., an increase in number, size and function of cells, the manifestations of the disease will be influenced to a considerable extent by this factor. Likewise, during the period of life when recessive growth is occurring, i.e., decrease in size, number and function of body cells, other manifestations may present themselves because of the different type of growth process. It must be pointed out in this connection that the human body shows both types of growth at any given period of life, that while progressive growth predominates during childhood, there are certain recessive changes taking place also and likewise during adult life after maturity, recessive growth predominates, there may be certain progressive changes occurring simultaneously. This important subject needs investigation in the light of more recent studies on the nature of growth.

3 The influence of race on the manifestation of rheumatic fever has been considered for many years, and recently important information has been developed on this point. While certain races seem to show a lower incidence of the disease,

It seems more probable that this is due to a difference in location rather than a difference in race. Recently Porto Ricans living in New York City have been found to show a high incidence of rheumatic fever, whereas when living in their native state the disease tends to be rare. A group of New York children with rheumatic heart disease, including several Porto Ricans were transplanted to Porto Rico for a year and during this period the signs of rheumatism disappeared. When these individuals returned to New York City the disease reappeared. Such studies tend to show that race is less of a factor than location.

4 The question of climate as a factor in the incidence of the disease has also been considered for a long time and at present is not solved. Rheumatic fever with heart disease is found more frequently in the north temperate zone throughout all parts of the world than in any other location. There is also an opinion that the disease is found infrequently in the southern parts of the United States, in the tropics and in similar climatic zones in the southern hemisphere. The disease is not frequent among the Chinese living in the north temperate zone nor is it frequent in South America and Africa. The few observations made in these remote parts of the world however do not entirely settle this important question and further study is needed.

* The social status of patients with rheumatic fever is generally low and in a recent report from Dr. Paul from New Haven it was shown that the disease occurred more frequently among Yale University students who had come from a lower social status. A definite opinion on this general subject, however, is not available and certainly it warrants further study. It is probable that important secondary factors enter largely into the high incidence of the disease in the lower social strata, for example, bad housing, frequent infections, close contact with bacterial carriers and improper care during minor illnesses, particularly ordinary colds. The importance of these secondary factors in the higher incidence of tuberculosis is well recognized and they probably play an equally important part in the higher incidence of rheumatic heart disease.

This covers the first two articles of the outline and Dr. Bachmann will introduce the discussion.

DR. HAROLD A. BACHMANN (CHICAGO)—I have not attempted to agree or to disagree with the things Dr. McCulloch has said in his paper but as I read it over I felt there were certain clinical factors which it might be well to review.

Dr. McCulloch's paper is so clearly conceived and so thoroughly logical that it is difficult to know where to begin this discussion. Of one thing I am sure that in the main most of us agree with the statements he has made and few will take serious issue with the conclusions he has drawn. In regard to the usage of rheumatism in our terminology I feel strongly that it should be retained. If nothing more it conveys to the laymen a striking symptom which should be urgently impressed upon them at all times. Our success in this field of cardiac disease in children still lies in its prevention, and without descriptive terminology we cannot attempt to accomplish our purpose.

It would seem to me, in spite of the completeness of Dr. McCulloch's definition of the rheumatic state, that there should be added some statement to the effect that the culmination of the entire rheumatic picture is definitely associated with environmental, climatic and hereditary factors. Without these, the rheumatic state, one might say, could not and does not exist.

I feel that one point further should be made regarding the rheumatic infection—once it has been inflicted upon a child we should never consider it as cured, but rather as in tuberculosis, consider it quiescent, or as an arrest of the process."

The broader view regarding the etiologic factors, as expressed by Swift, is highly commendable. It logically explains the bacterial differences of the past, and presents a working basis with which to start.

I am fully in accord with the opinion that malnutrition is an important contributing factor in the production of rheumatic infections. The question that comes to mind, however, is, should we stop here? I am convinced that there are contingent factors of environment which are equally important. Many of these have been strongly emphasized in the current literature. The contagious factor, and the indulgent care of the parents to minor infections should receive additional consideration and discussion.

In regard to the manifestations of the rheumatic state I feel that tonsillitis should be further qualified. Among ourselves and certain economic groups, it may be well to emphasize tonsillitis in relation to rheumatic heart disease. With the average private practice group this emphasis should be guarded. People are so health conscious these days that it behooves us to be careful not to add another worry to the now anxious pseudoscientific mother.

In considering joint and muscle pains I am sure we are all convinced of the importance of any arthritis symptoms in childhood. I do feel that every joint pain should be considered rheumatic unless otherwise proved. I wonder, however, whether one should assume a totally benign attitude toward growing pains. Fatigue, as stated, is a rational explanation for some, likewise is the disproportionate growth during adolescence. But eliminating both of these, can we entirely ignore the histories so frequently obtained?

In this connection, I am going to read the abstract of the paper which Levine of Boston is giving at the American Heart Association Meeting. "Recent years have seen concentrated interest in the streptococci as a possible cause of rheumatism. Recognizing the importance of this work, clinical experiences indicate that changes in the internal environment of the host must play a very significant role, and this aspect of the problem has received little attention. The strong familial factor which cannot entirely be explained on the basis of contagion and external environment suggests an inherent vulnerability. There is much we observe that points to changes in the endocrine balance as a factor in deciding whether an individual is vulnerable to this disease. The term 'growing pains' has more than colloquial meaning when the problem is viewed in this light, for thus it may be related to the endocrine system. It is also curious that chorea practically never returns after the age of twenty except under one circumstance, pregnancy. Here again the endocrine system is altered. Furthermore, there are frequent instances in which recurrent rheumatism appears in the same individual the same month of the year, particularly February. We now know that the weight of the endocrine glands alters during different months, and in February some of them are at a particularly low ebb. This may be a fruitful field for investigation."

Back in 1909, Sir Norman Moore said: "It would be very much more accurate to regard the carditis as the center of the infection and polyarthritis and chorea as complications. The joint lesions attract immediate attention by the pain they cause, the movements of chorea are not likely to escape notice, but it is the cardiac lesion which shortens life." All of us, I am sure, have had this dictum exemplified in practice, and further discussion of this phase would seem justified.

The mention of pneumonitis in association with rheumatic heart disease should stimulate an expression of opinion regarding the posterior lung findings in pericarditis. Certainly these findings cannot be entirely explained on the basis of effusion or compression. The clinical course prompts me to conclude that we are dealing here with a pneumonic process due to adjacent pathology.

Dr McCulloch makes the statement that during adult life the joint pains occupy a much more prominent part'—and further—"It is also well known that the chance for the heart to become involved during adult life is much less than during childhood." I have frequently been impressed with the same fact in children. In other words when the arthritis symptoms were most prominent and fulminating the milder was the resulting carditis. Is it that the infection spends itself here and thus lacks the potency to invade other susceptible structures?

The influence of race on the manifestation of rheumatic fever is sufficiently covered by Dr McCulloch's concluding statement in that studies tend to show that "race is less of a factor than location." I would, however, raise the point that in my experience the Italian child with heart disease shows the most remarkable come back of any race I encounter. Likewise that the Negro race, even in the North, seems less vulnerable to the rheumatic infection.

Much has been said regarding specific phases pertaining to the rheumatic state in childhood but the most important point to me is the social status of the patient. Were it and its contingent factors explained, I am sure we could forgo ahead with one of the most striking examples of preventive medicine known in history. Our success must lie in the prevention of heart disease among children, not its cure. If we could once analyze and explain these environmental factors we would begin to accomplish results. Why is there such a dearth of rheumatic heart disease in private practice and why such an abundance in our dispensary groups? Does sensitivity, allergy and heredity explain all? Certainly no field of investigation could be more fruitful and helpful than further study of the environmental factors pertaining to the rheumatic state and rheumatic heart disease in children.

DR McCULLOCH—One of the main ideas in these conferences is for each of us to express his own experience and the opinion formed as a result of that experience. By this all of us learn what others are doing. We would like to hear from as many as care to discuss any particular phase of the presentation thus far.

DR. T. D. GORDON (GRAND RAPIDS, MICH.)—Besides the ordinary chorea are there any other brain conditions which are considered as being rheumatic—meningitis for instance?

DR. ROBERT A. BLACK (CHICAGO)—I feel that a great many headaches in children might be looked upon as rheumatic in character. I personally have never seen meningitis that I would say was rheumatic. We all see many cases of chorea which resemble a mild encephalitis. In fact, I think it is hard to differentiate a severe type of chorea from encephalitis.

DR. BACHMANN—What prompted your question?

DR. GORDON—A case I recently saw—a child who had rheumatism, and who in my absence from the city was taken to the hospital with meningitis—2,000 cells mostly polymorphonuclears but no organisms were found on six lumbar punctures. This boy made a complete recovery without other treatment than salicylates.

QUESTION—Did you make cultures of the spinal fluid?

DR. GORDON—Yes and no organisms were obtained. I returned to the city after four or five days, and knowing the history of the case suggested the treatment and the boy made a rapid recovery without any residual signs from the meningitis.

DR. PHILIP ROSENBLUM (CHICAGO)—One should be very careful in interpreting a 2,000 cell count. The patient may have had an epidemic meningitis, that alone does not speak for rheumatic involvement of the brain. One might have rheumatism and also have a meningitis of other origin.

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Body weight alone does not constitute a good criterion of malnutrition even when considered in relation to body height. The obese child is frequently as much malnourished as one who is underweight. We have seen many children with chorea who are fat but on close examination it is easy to recognize that they are malnourished just as much as those who are underweight. Our impression is that chorea occurs in the obese type of older child more than in any other constant type. I seriously question whether rheumatic fever and especially the heart disease that goes with it will occur in a child who is in good nutrition. I do not mean that all children who are malnourished have or may have heart disease. It has been observed also that many tuberculous children are normal in weight and that the incidence of underweight among tuberculous children is very low but again in these studies, the sole criterion of malnutrition was underweight without regard to other manifestations of malnutrition. I think a full clear definition of nutrition would possibly help us a great deal in interpreting what constitutes malnutrition. There are certain other diseases like rickets in which the children are not always underweight but should be considered as malnourished.

DR W S GIBSON (CHICAGO)—What are the criteria for the determination of malnutrition in children?

DR McCULLOUGH—That is a rather difficult question to discuss at this symposium and in so short a time. Nutrition is the state in which living matter exists at any given time, resulting from the various processes of metabolism. As well as one can define this state in living children under ordinary conditions, the criteria are (1) an estimation of body weight with some other mass measurement in relation to body length or some other linear measurement using the many and varied tables that have been described for the establishment of normal or average ratios making allowances for those influences which deflect the individual from the normal or average (2) an examination of those parts of the body which are susceptible to nutritional changes and which are evident on ordinary physical examination the various qualities of the skin the amount consistency and distribution of subcutaneous body weight and the size tone and coordination of skeletal muscles (3) by some knowledge of the child's history in regard to environment type of feeding intake of necessary food elements reaction to infection and other general habits of play rest school etc. Farther than this the question becomes very complex and involves the determination of many points in metabolic and chemical laboratories.

DR ALBERT D KAISER (ROCHESTER N Y)—I want to say something about growing pains in contrast to fatigue pains. I have been interested in growing pains as to whether they are symptoms of rheumatic disease or whether they are all fatigue pains. I followed a number of children over a period of years with a history of growing pains and no other rheumatic symptoms. In this large group of children I found that 10 per cent of the children who had growing pains appeared later with some involvement of the heart in most instances not severe. They had a mild cardiac involvement yet severe enough to be classed in the group of children having rheumatic carditis. It is of course not certain that the growing pains were responsible for the cardiac involvement but it is suggestive that persistent growing pains are the result of an infection. I found that 8 per cent of the children examined in Rochester gave a history of growing pains. A higher incidence of growing pains has been reported from other cities.

I am not in absolute accord with the statement that rheumatism is influenced chiefly by the social environment. It plays an important part but another significant factor seems to be necessary and that is the element of infection. Those who have followed Coburn's work in New York have been impressed with his studies on

nurses, training in the Presbyterian Hospital. Before completing their course 30 per cent had developed some form of rheumatic manifestation. He concludes that it is not so much the change of environment for they had adequate food and rest, but because they were brought in contact with streptococcal infection which they had previously escaped. The incidence of rheumatic fever has been high in Rochester during the last two years. There has also been a high incidence of scarlet fever. *It was found that many children who appeared with rheumatism had scarlet fever within the last three years and the cultural studies of the throat flora showed a high incidence of hemolytic streptococci.* The evidence at hand seems to suggest that poor social environment plus contact with the streptococcus is a factor in the causation of rheumatism.

I believe the improvement noted in children sent to Porto Rico is due to the absence of streptococci in the throat. The streptococcus is probably the exciting cause of the disease but a susceptible host is necessary. The factor involved rendering the host susceptible is not known. It may be some enzyme or internal secretion that fails to function properly.

DR J R GERSTLEY (CHICAGO)—I have always been interested in the subject of growing pains. Every child seems to have them to some extent. When Dr Kaiser reported a history of growing pains in a large percentage of rheumatic children, did he have any controls?

Of course I realize that Dr Kaiser's study was not one primarily of growing pains. These were reported as purely incidental findings. However, growing pains are such a common complaint that I believe we should be somewhat critical as to their significance. For instance, if Dr Kaiser reports that 10 per cent of his cases of rheumatic endocarditis gave a history of growing pains, what percentage of a like number of children without rheumatism and endocarditis would give a history of such pains? If a number of much less than 10 per cent would be found, I grant the evidence would be in favor of a rheumatic significance to these pains. But I do believe there should be a control series.

DR McCULLOCH—In reply to Dr Gerstley's question, we have seen children in the clinic with rheumatic heart disease, oftentimes in an advanced stage with no history of pain in the joints, growing pains or any other kind of pain. The difficulty we have had is to know how to classify in an intelligent way the various pains these children may have. It is well known that they vary a great deal in degree, location and in many other characteristics. The well defined inflamed joint seen so commonly in adult life with the usual objective signs is relatively infrequent in younger children. Mention has already been made of the pain in the legs from flat feet and it may be pointed out again, the rather common pain in the legs from fatigue. These pains should not be considered either growing pains or rheumatism. The chief difficulty arises when a child is seen with tonsillitis, with signs of heart disease and with ill defined pains in the extremities. Such pains are probably due to rheumatism and should be so interpreted. I would like to insist again that mere growth should not produce pain in any form.

DR ROSENBLUM—One thing I would like to ask, is about erythema multiforme associated with arthritis, as a rheumatic manifestation. This association is more frequent than we realize.

DR McCULLOCH—The list of manifestations of rheumatism as given is, of course, not complete. I agree with you that erythema is a fairly common sign.

DR EPSTEIN—Skin lesions are certainly a manifestation of rheumatism. I think you see them in children who have rheumatic nodules if the skin is involved in some form by the rheumatic infection.

I hoped somebody would bring up the question of erythema nodosum.

DR G R WEINFELD (CHICAGO)—In reply to Dr Rosenblum's question, Swift pointed out that this was also a manifestation of very serious cardiac involvement. I have had about six cases under observation for about four years who have had erythema annulare. One boy has had it for about six years. He has no serious cardiac complications. At one time it appears as a coincident manifestation, its intensity depending upon the intensity of the infection. Then for a time the dermatitis disappears and again he will have the dermatitis without anything else. In one child with a severe heart lesion an erythema marginatum has been present for a long time. The other day I saw another child who had an erythema marginatum but I had not noticed it until I saw him in a strong light. I doubt very much whether it is a proliferative lesion. It has more the earmarks of an allergic manifestation. I think it is important that we all understand what we mean by this lesion.

DR ROSENBLUM—Rheumatic peritonitis may occur but surely not very often. The majority if not all of the cases were associated with pericarditis. We know one of the first symptoms of pericarditis is often pain in the abdomen, and not infrequently they get to the surgeon first who operates only to find a pericarditis later. We know these cases do not need operation. Surgeons usually justify their operation by stating there was a peritonitis. They never obtain positive cultures and all the cases heal without drainage.

I feel the majority of these so-called operated rheumatic peritonitis patients are just a mistaken diagnosis for beginning pericarditis. I question, too, the occurrence of real rheumatic pneumonia. I feel much as does Dr B. Gibson about the etiology of rheumatism. There is probably a specific organism as in tuberculosis with environment, diet, vitamins, climate etc. only secondary factors.

DR BACHMANN—I think Dr Kaiser mentioned a very important point 'exposure to germs.' We see this frequently in the form of epidemics. I think there must be something else associated—that is, the lack of proper attention to minor infections. The children we encounter in private practice receive attention for minor ailments and thus evade serious trouble. In the dispensary group these are ignored. I have felt that the indulgent care toward these minor infections, especially exposure to streptococcus, plays quite an important part.

DR J H WALLACE (OAK PARK)—All this confusion about some of these things prompts me to challenge Dr Bachmann's optimism about prevention. There is a good deal of conflict of opinion about race and hereditary and climate. In discussing malnutrition Dr McCulloch thought the definition should be emphasized. I feel the same way about prevention. The preventive phase of the problem as I see it is the following through in the prevention of the second attack or prevention of complications in the heart. If by prevention of rheumatism one means prevention of the first attack I cannot feel the optimism of Dr Bachmann since we are not agreed as to the exciting cause. It would seem that prevention strictly speaking would entail eliminating the predisposing factors—a rather gigantic task if it means changing racial and hereditary characteristics and bringing up the housing situation and hygiene of the lower social strata. One thing I might mention with regard to race and color is that it is very difficult to infect an African Negro with scarlet fever and the Chinese are only slightly susceptible. This might have something to

do with the fact that they are less susceptible to heart disease, since immunity to one streptococcal infection seems to involve immunity to other strains of streptococci.

DR BACHMANN—My optimism is simply the desire to educate the layman with the facts about rheumatism. The average parent who comes to us today with a child with heart complications has no idea as to what that might have come from.

DR WALLACE—That is probably correct. We cannot prevent rheumatism, however, until we know more about it. We can prevent the second attack. Strictly speaking, so far as the prevention of rheumatism is concerned, I wonder if we know enough about it.

DR BACHMANN—I feel that prevention will come before the cure, however.

DR GIBSON—Dr McCulloch has had control over his patients for a long time and I wonder if, after a number of years, these children have had definitely fewer recurrences than other children not so well cared for.

DR McCULLOCH—That is a hard question to answer. About five years ago, we reported the results of a study of a group of cardiac children who had been patients in our convalescent home. Much to our surprise, we found that the number of attacks of rheumatic fever in the children who had received such care tended to be rather high after discharge to their homes, in comparison with a similar group who had not been admitted to the convalescent home. We felt, however, that the child's general condition had been greatly improved and that when the subsequent attacks occurred, they were of shorter duration and there was less involvement of the heart. Our only explanation of this observation was that when the child returned to his previous environment, particularly if the environment had not been improved, exposure to farther infection resulted in attacks of rheumatism because his susceptibility had not been altered. The study led us to believe that convalescent care was of value chiefly during the time the child needed to be in a more favorable environment and also in rendering him more able to withstand subsequent infections. It still seems to us that the prevention of rheumatism lies first, in creating healthy children through the application of the broad principles of pediatric care, second, in taking care of children properly when they have an acute illness and, third, to be sure they are well of any infection before they return to school. I think these things lie distinctly within the field of pediatric care and have no more relation to cardiac problems than they do to other forms of disease. In this way, we will be able to prevent a lot of rheumatism.

DR J. C. McKITTERICK (Burlington, Iowa)—I am inclined to agree with Dr. Wallace as to the importance of prevention. When a patient comes to me with swollen joints I know he has rheumatism. He complains of stiff legs in the morning, has low fever, and fatigue, this leads me to believe that the child may have rheumatic heart disease. But what will prevent it? Until more work is done in the prerheumatic stage I think we cannot get very far.

DR KAISER—Might I state our own experience. We had the same feeling that individuals with rheumatic disease had low calcium and cholesterol values. We studied the blood lipids in 75 rheumatic cases, and found normal calcium values and the cholesterol was well within normal limits. They were low in the acute cases but they were also low in pneumonia and scarlet fever, but with recovery they returned to normal. Dr. Clausen studied the vitamin A content and the carotene in the same group but found no striking relationship between the rheumatic state and a deficiency of this vitamin and provitamin.

DR. McCULLOCH—Balanced feeding and proper dietary intake are of course important. A survey of the diet of many of these children shows a history of a predominating bread and butter diet with relatively little milk meat eggs and vegetables. The mother often explains that the child eats enough but runs it off, which is, of course not true. Unfortunately this same explanation is offered many times by physicians for the malnutrition underweight and fatigue which may be present. Activity should not produce malnutrition and it is probable that with satisfactory food and regulation of activity the child would not become thin. The improvement following administration of foods containing abundant calcium salts and cod liver oil often demonstrates that the diet was defective.

We now come to the third part of our presentation—*The Care of Children With Rheumatic Fever and Heart Disease*. It should be clear to everyone that the care of such children depends on the period in the course of the disease in which the patient finds himself. It is probable that a lack of consideration of this important subject accounts for the widespread divergence of opinion which exists in the minds of most of us and for the unsatisfactory directions for care that most patients receive. Measures which are applicable at one time would be inappropriate at others. It is suggested that four important periods in the course of the disease should be considered (1) The period of active infection (2) convalescence (3) quiescence (4) when the process is healed or when it has disappeared and the patient is cured.

1. During the period of active infection evidence of activity must be sought and recognized. The three important points of evidence would be active focal infection in tonsils, sinuses or in any location, fever and rheumatic nodules. So long as cervical glands remain enlarged the tonsils show evidence of redness edema, thickening and pus or so long as the mucous membrane of the nasopharynx shows hyperplasia, redness, edema etc. the patient must be considered to be in the period of active rheumatic infection. Also so long as the body temperature remains above normal or shows extreme daily variations the patient should be considered in the period of active infection. Leucocytosis and joint pains are of value when they are present to a marked degree but in the usual child their absence or presence is not of great assistance in determining the period of infection. Rheumatic nodules, however are definite evidence of an active infection and so long as they remain it must be assumed that an active process is going on in the heart. During the period of active infection treatment should be directed toward the control of those manifestations present. It is important during this period to clean out foci of infection as soon as it is determined that the patient can stand the necessary procedures. The use of salicylates and other drugs relieves fever joint pains, and many other toxic manifestations. It is also important during this period to provide rest for the body and heart as much as possible. This important measure cannot be overemphasized even though it is briefly stated here. If congestive failure of the heart occurs during this period it is of grave prognostic significance and should be a matter of first consideration. So long as the heart muscle is unable to do its work, it is futile to undertake other remedial measures.

2. It has always been difficult to decide accurately when patients are getting well and are convalescent. In a disease like rheumatism where the symptoms and signs are so varied and irregular it is very much more difficult than usual. Some of the difficulty arises from the fact that few criteria are available to determine accurately the absence of infection. It has been suggested that a normal temperature and heart rate together with a good appetite should indicate recovery from any infection. These statements should hold true for children with rheumatic heart disease. In addition children should show no signs of fatigue should be gaining in body weight and height and should be free of active infection in tonsils and

elsewhere. Other criteria such as the absence of leucocytosis, changes in the heart signs, etc., are also easily applied to the individual child during the period of convalescence. Graduated return to normal activity and function should be undertaken. Whether or not this period is short or long will be determined by the degree of injury occurring in the heart and body during the attack. It must be pointed out that there is a tendency to err on the side of a convalescence too short rather than too long, and in case of doubt it is safe to delay the convalescence.

3 By far the largest number of children with rheumatic heart disease are found in a period of quiescence. While those under the care of a physician are generally in the period of active infection or are convalescent, surveys show that a very much larger number may be found in school and not under the care of physicians. This very important group needs careful study and control. These children will be found on periodic health examinations, at school, and when under the care of physicians for some intercurrent condition. It is an important group to recognize, since remedial measures will yield larger returns than in almost any other group under consideration. These children are not ill, but their health is impaired, the chances for a return of the rheumatic fever are good, and the ultimate prognosis for their reaching healthy adult life is poor. Educational measures by individuals, organizations and institutions will uncover a large number of these children.

Their care consists of a regulation of their daily routine so as to provide a proper balance of activity and rest. When possible they should be allowed to attend school or be at work, and to undertake jobs which are within the limit of their performance. Since most of these children are in Class I, they probably need more of an adjustment of their physical activity than a restriction of such activity. Such a program seems desirable, because it allows the child to live more nearly normal than when restricted in any fashion, and probably is of greatest value because such children must be fitted for their life work. Unless they can learn their limitations they probably become maladjusted both mentally and physically and acquire an unusual outlook on life as well as their inability to support themselves. It also is important during the long period when such children remain quiescent to provide proper measures for good general health. By this is meant proper food, proper amount of sunlight and fresh air for play and rest, and enough sleep, and the importance of a quiet environment must be emphasized. That this factor is of some importance is borne out by the high incidence of chorea in children living in congested, noisy sections of the city.

4 Evidence is available that children with rheumatic fever and heart disease may recover entirely, so that at subsequent periods no evidence of disease can be made out. A larger group definitely are known to live for long periods without recurrence of their rheumatic fever or heart disease. Many of these have been known to live throughout the remainder of a normal span of life, with full physical activity and earning power, with no further heart disease. While this number is relatively small in comparison with the total number of children with heart disease who die early, it is sufficiently great to warrant special consideration. This opportunity rarely comes to the pediatrician because the problems involved are a part of adult life. The part for the pediatrician to know, however, is that there is some reward to offer the cardiac child for carrying out the directions. Unless this reward can be pointed out, the child may have very little to look forward to and no incentive to carry out instructions. The probable chance of recurrence of a myocardial, endocardial or pericardial lesion is always great. Such children must be treated more carefully when infections occur than individuals who have not previously had attacks of rheumatic heart disease. They must be told they will always require special protection. Children suffering from mitral valvulitis particularly when stenosis has occurred, have a bad prognosis, and Cotton has shown that 90 per cent

of such children are dead after a period of ten years from the onset of their disease. Contrary to the usual prognosis of patients with syphilitic aortitis and aortic insufficiency when the prognosis of life is not greater than three to five years, children with rheumatic aortitis and aortic insufficiency uncomplicated by mitral stenosis seem to live and do well, provided the active infection disappears. It has been pointed out by Dr. Conner that such individuals may live several score years without cardiac distress.

DR. BACHMANN.—On the care of children with rheumatic fever and heart disease I am sure we are all agreed. Agreed at least so far as fundamental principles are concerned though we may disagree on details. However, until facilities are generally available where patients with the varying degrees of rheumatic infection can be cared for complete success cannot be obtained. My feeling is that the chronic cardiac cripple receives too much attention while the milder types and those still considered potential receive too little. The only solution to this question rests in the establishment of more homes or sanitariums for the chronic or perpetual rheumatic thus making available for the others more beds and more extended care. I find myself frequently discharging patients with a promising future and retaining those with none—only because the ward is crowded and something must be done about it.

In ascertaining when the acute stage of rheumatism has subsided, I feel that no greater display of the art of medicine exists. We all have clinical criteria upon which we pin our faith but upon final analysis experience, observation and intuition are the factors which guide us most. Among the more recent criteria pronounced as valuable, is that of Bernard Schlesinger in a study of the sleeping pulse rate in rheumatic children. I would like to inquire if any of you have used this method and how reliable it has appeared to be. Personally I attempted it but gave it up before a definite conclusion could be reached. To me the most convincing evidence of heart improvement and integrity whether in the hospital or in the clinic has been weight maintenance and gain. No other functional test in my experience, is more easily obtainable or more reliable.

DR. BLACK.—In answer to Dr. Bachmann's reference to Dr. Schlesinger's observation on the pulse change between the sleeping child and the child awake. Dr. Schlesinger showed many cases in which his night and day pulse ratio proved the correctness of his statement. At La Rabida Sanitarium we found it to be correct but it was not observed as frequently as Dr. Schlesinger seemed to find. We take a midnight pulse in the Sanitarium and find in chorea the reverse is true in chorea a very high day pulse with a low night pulse the spread of the pulse rate becoming much less as the chorea improves.

Dr. McCulloch does not feel as enthusiastic about the Sanitarium as I do. We have had about 1500 cases go through the Sanitarium. We do not have as good a follow up system as Dr. McCulloch has.

The physicians treating tuberculosis made great advance in arresting the disease when they instituted sanitarium care. At La Rabida Sanitarium we have adopted much the same régime as is followed in a tuberculosis sanitarium. High calorie feeding with much rest and carefully supervised exercise. Until we know more about the etiology and specific treatment of rheumatism I think we would do well to stimulate sanitarium care. You educate the child and the parent as to the true nature of the disease. You are able to detect the slight relapses. Slight upper respiratory infections are often followed in seven to twenty-one days by a recurrence of rheumatism. A rheumatic child who has a slight upper respiratory infection would in my opinion, be much improved if kept in bed until all symptoms disappear which is usually between two and three weeks. Do you not think that by such treatment the later mortality would be much lowered?

DR GERSTLEY—I, too, have been trying the Schlesinger test on cardiac children. Those who are recovering seem to have diminution of the pulse rate at night. On the other hand there are a number of fallacies in that test. When you ask the nurse specifically to take the pulse, she is likely to go at it so energetically that she wakes up the child. You must be sure that the child is asleep when the pulse is taken. Whether the interpretation of the drop in the pulse means that the infection is over is another question.

DR BACHMANN—It seemed to me that the count of ten which is supposed to be the difference between the alert pulse and the sleeping pulse, is too narrow a margin to be reliable.

DR WEINFELD—I wonder whether Dr Kaiser would tell us about his experience at Rochester with tonsils. I would like to ask if there have been any ill effects from the removal of tonsils at the improper time.

DR KAISER—Personally, I am opposed to it, and so it has been done only occasionally. I believe the results are unfavorable. I do not have the data on that.

DR WEINFELD—When do you feel that tonsils should be removed?

DR KAISER—I have been interested in the relation of tonsils and rheumatism. I remember the old textbooks said that the way to prevent rheumatism is to take out the tonsils. When the opportunity came to observe a large number of children that was the first thing I studied, and in my opinion there is no great relationship between tonsils and rheumatism. The important thing in favor of tonsillectomy is that a great number of children are spared throat infections by having an early tonsillectomy. Again, statistics are very misleading. We have tried to approach the study from all angles in comparing a large number of children over a long period, those who were and those who were not tonsillectomized. We found 30 per cent less rheumatism in those who had been tonsillectomized—that is, 30 per cent of those children were protected against rheumatism. On the other hand, when we studied the children who had rheumatism, mild or severe, and were tonsillectomized, we could not prove a thing. However, that is my personal experience. I have a letter from Dr Poynton in which he states he could not prove that tonsillectomy had any bearing on rheumatic attacks, but clinically he saw so much difference that he recommended tonsillectomy. I think I feel the same way.

DR McCULLOCH—We have been interested in a problem that is related to tonsillectomy. We have noted occasionally that a child who is either convalescent from or quiescent after an attack of rheumatism, within a week or ten days after operation for the removal of tonsils and adenoids will have an attack of rheumatic fever or chorea. Following the suggestion of Dr Cameron several years ago, we instituted the procedure of giving salicylates before operation and continuing them daily for a week or ten days afterward, the idea being that salicylates would probably prevent in some way the rheumatic fever attack following tonsillectomy. It seems to us that the children do not react so much when salicylates are administered in this way.

QUESTION—How do salicylates act in preventing the attack of rheumatic fever?

DR McCULLOCH—I do not know. Nor is it known how they affect any manifestation of rheumatism.

DR EPSTEIN—The chairman did not go into detail concerning the manner of administration and the dosage of salicylates. I get satisfactory results by

giving large doses, 150 grains, per rectum and repeating when necessary. I should like to ask whether this method is preferable to administering smaller doses orally over a longer period of time.

DR. BLACK.—In cases of active acute rheumatism I give from 40 to 60 grains of sodium salicylate by rectum for three to five days, then continue with 9 to 10 grains three times a day for six months.

DR. A. L. NEWCOMB (CHICAGO).—I cannot help but wonder when we talk about prevention of rheumatic fever if treatment and prevention are not much alike. Physicians do not see the children much in rheumatic fever. The parents call up and directions are given to put them to bed and usually salicylates are given. Sometimes the mother says, "I have you every time she has a temperature yet here is a neighbor child who is playing out in the dirt and mud and is never put to bed with a cold." Yet it is the neighbor child who develops rheumatic fever. I am usually very careful as to how soon the child is allowed to get up. If the parents did not call for medical advice the children would be up and around in a few days. It is hard to separate prevention and care of the rheumatic state.

DR. McCULLOCH.—We now come to the fourth article—*The Relationship of Rheumatic Fever and Heart Disease in Children to Heart Disease in Adult Life*. This important question has not been solved. Even the usual heart specialist is not familiar with the initial stages of heart disease in children nor does the pediatrician frequently have an opportunity to observe his patients over long years into adult life. The evidence at hand today is chiefly of the put together variety and is very unsatisfactory. It would be desirable if a large group of physicians, particularly pediatricians, could observe patients in adult life whom they have studied as children, and in this way learn something of the late effects of heart disease. The following points may be mentioned for discussion.

1. It would be important to note the number of adults with healed rheumatic heart disease who show recurrences of activity. It was suggested by Dr. Morse that chronic cardiac valvular disease should not be considered as rheumatic heart disease and that an individual who once had rheumatic heart disease may lose all evidence of rheumatism. However the nature of the heart disease is such that its etiology can usually be recognized no matter at what time of life the patient is seen. It is true that when the active infection in the heart and the rest of the body has disappeared the process in adult life is not similar to that seen in childhood and presents the picture usually described as chronic cardiac valvular disease but the origin of the lesion is rheumatic. Proliferative lesions of the aortic and mitral valves are always important and when destructive changes in the heart muscle have taken place, an injury of a permanent type results. No matter at what period of life the patient may be seen subsequently he will always tend to show characteristic signs and tendencies in the course of the disease.

2. Subacute bacterial endocarditis occurs most frequently in young adults who have either a congenital malformation of the heart or more frequently no old healed or inactive rheumatic heart disease. Indeed a question has been raised as to whether no individual whose heart is normal would ever acquire subacute bacterial endocarditis. There is very little evidence to support such a supposition. Certain investigators believe that the differentiation between subacute bacterial endocarditis and rheumatic heart disease is not great and that they are the same process. The more general opinion, however, is that they are distinct processes and the subacute bacterial endocarditis is superimposed on the old healed rheumatic heart disease. The usual organism involved in such an endocarditis is the *Streptococcus viridans* though instances of staphylococcus, meningococcus, gonococcus and pneumococcus infections have occurred. It should be pointed out that in young adults with a

history of a rheumatic lesion who have fever and signs of infection, this important form of heart disease should always be considered. It is the usual cause of cardiac death in patients with congenital cardiac malformation, who are free of congestive failure.

3 Myocardial failure during adult life as a result of intercurrent infections or physical strain, particularly during athletic activities, may bear a definite relationship to an old myocardial injury received from a rheumatic infection or from other similar infections, such as scarlet fever, pneumonia, influenza and possibly from diphtheria. There seems to be little evidence that congenital syphilis affects the heart in such a way as to be responsible for myocardial failure in later life. Dr. Warthin, however, pointed out that sudden death may occur in adult life as a result of a congenital syphilitic infection. This idea has not been borne out by other investigators. The evidence available today suggests that most heart strain occurring in adolescence and early adult life can be traced directly to a history of rheumatism or other similar infection. Investigation of this relationship between the two periods of life should yield important information that would be useful to the pediatrician in directing a child who has had joint pains with or without heart disease.

4 Coronary heart disease which includes coronary thrombosis, infarction and occlusion, may occur as a result of circulatory changes in the heart muscle and vessels or as the result of senile changes going on in the body, but it has been suggested that these changes occur more frequently in individuals who give a history either of a high incidence of heart disease in the family or of rheumatic fever or a similar infection during early life. Coronary thrombosis may be a circulatory accident occurring more frequently in obese individuals under great mental and physical strain and bears no relationship to previous heart disease. Since coronary heart disease is an important cause of death, in adult life and particularly among individuals in the higher walks of life, it would seem important to determine the relationship between it and heart disease during childhood. At present this relationship does not seem to be very close.

Pediatricians have a large part in the prevention of rheumatic fever, by seeing that children are properly fed and cared for through childhood illnesses, and the mothers become intellectually rich if not financially rich through what we are able to tell them. It is a matter of intellectual status rather than economic status.

DR BACHMANN—I would like to emphasize, in conclusion, one factor regarding the pediatrician, not only in relation to heart disease, but also other chronic ailments of childhood, to say nothing of adolescence. We must extend our range so far as age is concerned. Without this we can never estimate the relation of rheumatic fever and heart disease in children to heart disease in adult life. Neither can we understand the influence an early nephritis has upon the adult. Nor will the adolescent boy or girl receive the intelligent support and guidance so highly necessary at this period. We need adolescent wards, dispensaries and physicians, and it is up to us as pediatricians to demand this extended service and prepare ourselves to handle this now neglected field.

DR McCULLOCH—Doctors particularly interested in rheumatic fever and heart disease who have had the opportunity to follow these rheumatic individuals from childhood into later life are very rare. When the child has been under the care of a general practitioner, he has either overlooked the relation entirely or has failed to recognize the heart lesion. As a rule the information we get from any source is not reliable.

DR BACHMANN—At the present time I am having that opportunity, but I am afraid that I have not been following them long enough to present data of

real value. After the patients leave the Children's Memorial Hospital I have been following them at St. Luke's dispensary to the age of eighteen or nineteen. The one outstanding thing I have noted is that the compensated mitrals and aortics in early childhood seem to have good tolerance and capacity until they get to about sixteen or seventeen and then they suddenly die. That is the only striking thing I have been able to observe up to the present time.

DR. EPSTEIN—I have not had this experience. The fact that about the age of twelve, children are transferred from the Pediatric Department to the Cardiac Clinic makes it difficult for the pediatrician to follow cases through adolescence. I think that the only way we pediatricians can determine the subsequent condition of our patients, is by keeping our files and inquiring from time to time as to the general status of their health. Recently Dr. Morse checked up by this method on one hundred cardiac cases which he had previously examined thirty to thirty-five years ago. In some clinics, especially in general hospitals which have cardiac departments, I think that it is a mistake to send these patients to the cardiologist. I would rather have the cardiologist come to the pediatric clinic thereby benefiting by his suggestions and at the same time watching the progress of the patient.

DR. McCULLOCH—Dr. Luecke, I would like to ask you a question. Is heart disease frequent in Dallas? and do you think it occurs among children living in western Texas?

DR. P. E. LUECKE (DALLAS)—I have been practicing there for about ten years and I have seen I think four or five cases of heart disease and to my knowledge no important cases of rheumatic fever at all. I have seen growing pains and occasionally sore joints which probably were due to a mild rheumatism which rapidly cleared up without cardiac involvement. The cases of cardiac involvement I have seen have not been associated with rheumatism, and of the four cases that I recall of cardiac involvement one occurred in a child about sixteen months old who is now eight years old and the murmur is fast disappearing. He had no relapse. The second, in a child two and a half years old, ran a precipitate course and the child died in about four weeks. One other is on the Pacific Coast at this time. I saw him at about four years, off and on for five years, and he was subchronic—highly nervous with twitchings which were never choreic; the heart was never compensated; the pulse was slow. I do not recall the details of the fourth case. We do not see many cardiacs in the hospitals there and do not have the problem of bed space taken up by chronic cardiac cases. I have seen three cases of paroxysmal tachycardia in youngsters, which we thought due to repeated nose and throat infections—bad tonsils. After tonsillectomy they gradually improved. I have not heard from them for the last two or three years and do not know what developed. I do not know whether that had any effect on the rheumatic infection. The cases of rheumatic fever and heart involvement are comparatively rare.

DR. McCULLOCH—Do you have many children with bad tonsils?

DR. LUECKE—I saw one the week before I came up, but we do not see many.

DR. McCULLOCH—I am always very much interested in hearing someone from regions of the United States like Texas, as to whether these conditions occur in those regions and to what extent.

The meeting adjourned at 4 45 P. M.

and beautiful hall. The official dinner of the Congress was held at the Mayfair Hotel, speeches being made by Sir Hilton Young—the Minister of Health—Dr Still, and Sir Thomas Barlow. After this function the Government gave a reception at Lancaster House, now the London Museum, which formed the setting for a very beautiful and impressive scene. The guests were received by Sir Hilton Young, on behalf of the Government. The Royal College of Physicians had an afternoon reception, the President, Lord Dawson, receiving the guests, and Lord and Lady Howard de Walden kindly entertained members of the Congress at tea in their home, Senford House. Sir Gomer Berry and the Board of Management of the Infants' Hospital, Vincent Square, gave a reception in the hospital, and afforded an opportunity of viewing the beautifully arranged new wing just being completed.

Dr George F. Still is retiring shortly from his hospital engagements, and it has been decided to recognise his retirement in an appropriate fashion. It is proposed that a cot be endowed and named after Dr Still at King's College Hospital, where he has for so many years worked as physician in charge of the Children's Department. Mr Gerald Kelly, an eminent artist, has promised a portrait of Dr Still, provided that a certain specified sum be subscribed for the cot. Dr Still, who was President of the International Pediatric Congress in London this year, is, as is well known, a pioneer of pediatrics in this country, and his retirement from hospital engagements will be deeply regretted by all his colleagues.

The British Medical Association held its annual meeting this year in Dublin. Dr T. Gillman Moorhead, Regius Professor of Medicine at Trinity College, Dublin, being this year's President. Dr Eric Pritchard was President of the Children's Section. The meeting was a great success, and our Irish colleagues exceeded even their usual great hospitality.

KENNETH TALLERMAN, London
September 11, 1933

Comments

THE relationship between pediatrics and the 'Child Guidance' clinic and movement is gradually reaching a sound and satisfactory basis. Viewed from a broad educational standpoint the child guidance movement has been a success, as it has brought needed emphasis upon the importance of the child's behavior and emotional adjustment as well as the physical side of his development.

While the value of the clinic as a propaganda and educational measure can not be questioned, the maintenance of such an organization as a distinct and separate entity divorced from the established fields of medical activity except in certain specific situations, is neither logical nor sound. The make-up of such an organization composed of a pediatrically minded psychiatrist, psychologist, and social workers has proved its value. Such a group attached to a school system for the study and handling of children with educational problems is desirable for every school system where the value of its potential service is commensurate with the cost.

To set up such an organization as an independent medical unit is quite a different matter. To begin with, the vast majority of behavior and emotional problems particularly those of young children, are not in themselves potentially psychiatric and thus elaborate study and treatment by such a group is not only unnecessary but entails a cost in time and money which cannot be justified. On the other hand in many older children conduct and educational problems arise which require a detailed study and treatment that can only be given by such an organized group as the child guidance clinic.

The minor or less important guidance problems and particularly those of the younger children are distinctly pediatric problems. These should be handled in a routine way by the physician and the emphasis should be on their prevention. It is much easier to prevent a behavior problem than to correct it, and the vast majority may be easily foreseen by the physician who is alert and has this phase of child development in mind.

That more serious problems will arise however is just as true as the fact that serious health problems arise in the child who has received competent medical supervision from the time of birth. These problems often call for services of the technically trained surgeon, otologist or neurologist, for example to make a correct diagnosis and to outline and carry out the required therapy. The child guidance clinic has a similar function in its own particular field. To separate such an organization from the rest of the medical body however is to limit its usefulness and value. Coordination and cooperation with the medical group as a whole is the best way in which the child guidance clinic may develop its influence as well as fulfill its opportunities.

The pediatric clinics as a whole are rapidly recognizing the importance of a special group within their organization for the handling of difficult conduct problems. This is the logical and sound place for a child guidance clinic. Where such a situation or "set up" has been created the rapidity with which the pediatric

clinic has become psychiatrically minded is amazing. What is more important than the work of a child guidance clinic per se which can only look after a small fraction of the problem children and whose work is chiefly therapeutic, is the influence of such a clinic in the pediatric group. Thus situated its influence extends to medical student, house officer and graduate student. It is upon these individuals in the ultimate analysis that the prevention of behavior and conduct problems will depend.

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There is a marked difference between halibut-liver oils that are stabilized against oxidative changes and those not so protected. The process designed to give this distinctive feature to the Squibb preparations (essentially the addition of the anti-oxidant hydroquinone) has been covered by registered patent (U S Patent 1,745,604). Physicians will be interested in the advantages of these Squibb products.

1 Stability of Potency—Laboratory tests prove the great advantage of keeping these fat-soluble vitamin products free from oxidative change. When unstabilized halibut-liver oil is exposed to oxygen in open containers for a few weeks, the Vitamin A content is reduced remarkably below the original potency. The same test applied to stabilized oil shows this process of destruction is greatly retarded. Much less of the Vitamin A content is lost over the same period. Therefore, the importance of this relative stability as a safeguard against vitamin loss is worthy of emphasis.

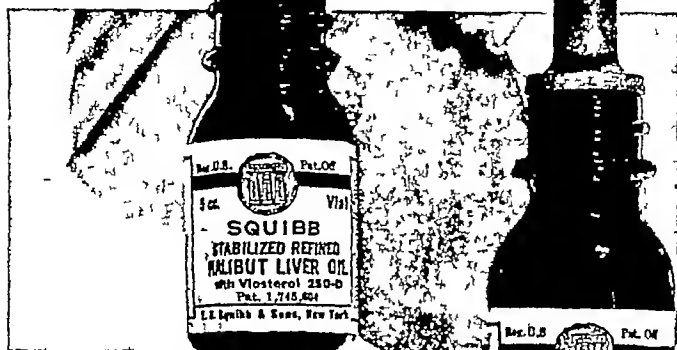
2 Greater certainty of results—With Squibb stabilized and refined halibut-liver oil preparations, the physician may feel more confident of constant and dependable results. He may realize to the full the possibilities of these extraordinary, highly potent, vitamin products. Stabilization is designed to give the physician halibut-liver oil preparations providing uniform and dependable dosage.

3 More Palatable—Crude halibut-liver oil usually has an acrid, disagreeable taste and odor. It may contain a relatively large amount of free fatty acids. This makes it less acceptable for satisfactory routine use. Halibut-liver oil preparations are therefore refined to ensure pleasant odor and taste. But here's the difficulty! If refined oil is not stabilized, the disagreeable characteristics are likely to return. The oil will again become unpalatable. Stabilization helps protect the acceptable quality of these products which makes them easy to administer.

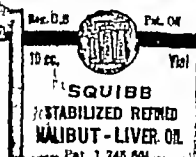
why physicians should specify

Halibut-Liver Oil

Plain and
with Viosterol 250 D



STABILIZATION is an important feature of these two halibut liver oil products by Squibb! They are kept potent, pleasant in odor and taste by a special process. When you prescribe halibut liver oil either plain or with Viosterol 250 D, always specify Squibb's!



The new place of Squibb stabilized refined halibut liver oil in prophylaxis and therapy

Halibut Liver Oil unfortified Because of the extraordinary richness of Squibb Halibut Liver Oil in Vitamin A, it should be considered by the physician who desires a relatively large amount of this important factor for growth promoting and for aid in building general resistance. It has found a fertile field as a prophylactic for infants. Easy to administer by drop dosage, it has also been used extensively for children and adults who may need a building up measure routinely. Squibb stabilized refined halibut liver oil has 80 times the potency of a cod liver oil containing 400 U.S.P. units of Vitamin A per gram. Each gram contains not less than 32,000 U.S.P. units of Vitamin A.

and not less than 2,000 A.D.M.A. (200 Steenbock) units of Vitamin D.

And with Viosterol Squibb stabilized refined halibut liver oil is also supplied fortified with irradiated ergosterol. This raises the Vitamin D potency to 250 times that of the standard cod liver oil defined by the Wisconsin Alumni Research Foundation. The richer product enables physicians to give relatively large amounts of Vitamins A and D in relatively small dosage. It offers untold possibilities for prophylaxis and therapy. (Each gram of Squibb Stabilized Halibut Liver Oil with Viosterol 250D contains not less than 32,000 U.S.P. units of Vitamin A and not less than 33,333 A.D.M.A. (3,333 Steenbock) units of Vitamin D.)

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\$240,000,000 a Day
Devoted to Destruction
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THE money the World War cost *for a single day* would build in each of our 48 states, two hospitals costing \$500,000 each, two \$1,000,000 high schools in each state, 300 recreation centers with gymnasium and swimming pools costing \$300,000 each and there would be left \$6,000,000 to promote education. The total cost *per day* for all countries was \$240,000,000. This means direct expense and does not include destruction of civil property.

Study the following table

U S Appropriation 1920

1	Past Wars	- - -	\$3,855,482,586—	68%
2	Future Wars	- - -	1,424,138,677—	25%
3	Civil Departments	-	181,087,225—	3%
4	Health Research and Education	- - -	57,093,661—	1%
			<u>\$5,686,005,706—</u>	<u>100%</u>

A physician knows how urgent is the need for money for public health activities. We cannot get it because of the billions poured down the rat hole of war, actual or prospective.

How to Stop War

Can it be stopped? Yes, of course. Peace machinery is already set up. It never existed before. It can be made to operate only by mobilizing public opinion behind it. That is what World Peaceways is doing, nationally now—but later internationally. We have reached millions of readers with our full-page

message during the past few months.

We are agitating for a Department of Peace at Washington. It will publicize all international issues—will take over the work we are now doing and do it on a larger scale. Write to your Congressman about it. Isn't a dollar spent for Peace worth \$100 spent for War? We'll never get Peace by wishing for it. We've got to work for it. If our program appeals to you, lend us a hand.

Send Us a Dollar

to carry on our work. Let's get rid of War. Let us make it as obsolete as dueling, as slavery, as using skull mould for medicine.

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Here is my contribution. I am showing your appeal to friends with the hope that they too will respond.

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With this richer cod-liver oil .

- *Extra Vitamin D to help babies build their bones strong and straight
their teeth sound and well spaced*
- *Adequate Vitamin A to promote growth and help build up resistance*

WHEN you are providing the important anti rachitic factor Vitamin D for babies don't overlook the necessity for ensuring them enough of another factor daily—*Vitamin A!*

Mendel in a review of this important vitamin calls attention to the many references to Vitamin A as "the first line of defense against the invasion of bacteria."

It seems necessary to provide babies with an abundance of this factor as well as Vitamin D regularly every day!

And now a specially enriched cod liver oil Squibb's 10 D Oil offers an excellent means of doing so!

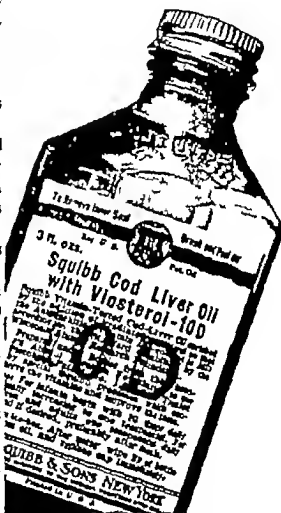
This cod liver oil to which Viosterol has been added supplies *ten times* as much of the anti rachitic factor as standard cod liver oil defined by the Wisconsin Alumni Research Foundation. Each gram contains 1333 A.D.M.A. (133 Steenbock) units of Vitamin D.

In addition it is a rich source of Vitamin A. Squibb's Cod Liver Oil with Viosterol 10 D provides an abundance of this valuable factor which promotes growth and may also aid in building resistance. It contains 700 U.S.P. units of Vitamin A to each gram.

Babies will grow better remain in better health as a result of receiving *both* these essential vitamins daily. Don't fail to give them the advantage of both regularly.

Now—for young babies—this improved anti rachitic measure—Squibb's Cod Liver Oil with Viosterol 10 D.

For older children—Recommend Mint Flavored 10 D for use every day! They will like the flavor and it will help keep up their resistance this winter!



SQUIBB'S COD-LIVER OIL with VIOSTEROL

LAIN
ORMINT AVOED

Manufactured under license from the Wisconsin Alumni Research Foundation and accepted by the Council on Pharmacy and Chemistry A.M.A.

Two Growth-Promoting Foods

for children allergic to certain food proteins

Leading medical authorities now agree that the proteins of milk, cereals, and eggs are responsible for most of the allergies of infancy. But until recently it has been virtually impossible to withdraw these offending proteins, for lack of a substitute containing other proteins of a kind and quantity adequate to maintain normal growth. Now in Sobee and in Cemac the physician has his choice of two such foods, either of which can be administered as the exclusive diet for infants.

SOBEE

A Diet Free from Animal Protein

Sobee is a soybean product consisting of 61.0% refined soybean flour, 19% olive oil, 9% arrow-root starch, 6% Dextri-Maltose, 4% dicalcium phosphate, and 1% sodium chloride. When Sobee is reliquefied with water and Dextri-Maltose No. 2 is added, the analysis in many respects approximates that of the usual cow's milk formula. Supplemented with cod liver oil and orange juice, it will maintain infants over an extended period as the sole source of food. The flavor of Sobee has recently been improved, so that infants take the mixture readily and gain normally.

Levy and Finkelstein¹ state that 38 of 40 infants sensitive to milk proteins showed definite improvement when placed on a Sobee diet. Klein,² Rowe,³ Clarke,⁴ and others report equally good results. Hill, describing the treatment of 80 eczematous infants with Sobee, observes that results were remarkable in some instances; severe eczema disappearing within a few days.



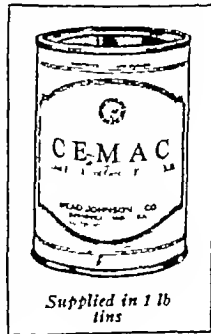
Supplied in 1 and 4 lb tins

CEMAC

A Diet Free from Cereal, Egg and Milk

Many children are sensitive not only to milk proteins but to those of eggs and cereals as well. If the allergic infant is placed on a diet of Cemac, any or all of these proteins can be withdrawn without danger. A mixture of beef, cauliflower, tomatoes, carrots, spinach, cane sugar, Dextri-Maltose, olive oil, cod liver oil, dicalcium phosphate, and sodium acid phosphate, Cemac is designed to supply all the nutritive requirements including vitamins C and D, for normal growth of infants. Cooked, strained, and homogenized, Cemac is ready for immediate use after dilution with boiled water. It may be fed from the nursing bottle or as a soup. Like Sobee, its analysis is similar to that of the usual milk formula.

Since 1925 Cohen and his associates⁵ at the Asthma, Hay Fever, and Allergy Foundation, Cleveland, have been feeding allergic children on this vegetable soup. "Allergic infants," Cohen reports, "thrive on this diet. In the vast majority the allergic symptoms disappear."



Supplied in 1 lb tins

¹⁻⁵ Bibliography on request.

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The Journal of Pediatrics

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"For those who are UNDERWEIGHT"

AT THIS season of the year when bodily resistance is at its lowest ebb and so many patients—particularly little children—are underweight, it is well to remember that Maltine With Cod Liver Oil has been prescribed by physicians for more than 50 years to correct those very conditions. One physician* writes us, "For those who are underweight I prescribe Maltine With Cod Liver Oil."

While the value of cod liver oil as an aid in building up resistance and weight is thoroughly recognized, it is a matter of concern to physicians that plain cod liver oil is not well tolerated by some infants and children. Maltine With Cod

Liver Oil, on the other hand, is well tolerated and easily assimilated by all ages.

Containing, as it does, 70% Maltine—a concentrated liquid extract of the nourishing elements of malted barley, wheat and oats—good sources of vitamins B and G, and 30% pure, vitamin-tested cod liver oil of high potency in vitamins A and D, Maltine With Cod Liver Oil is not only rich in the four vitamins, but in other elements essential to health and growth.

Maltine With Cod Liver Oil is biologically standardized and guaranteed to contain four vitamins—A, B, D and G. When administered in either orange or tomato juice, vitamin C is added. Biological report sent to physicians on request. THE MALTINE COMPANY, Est. 1875, 30 Vesey Street, New York, N. Y.

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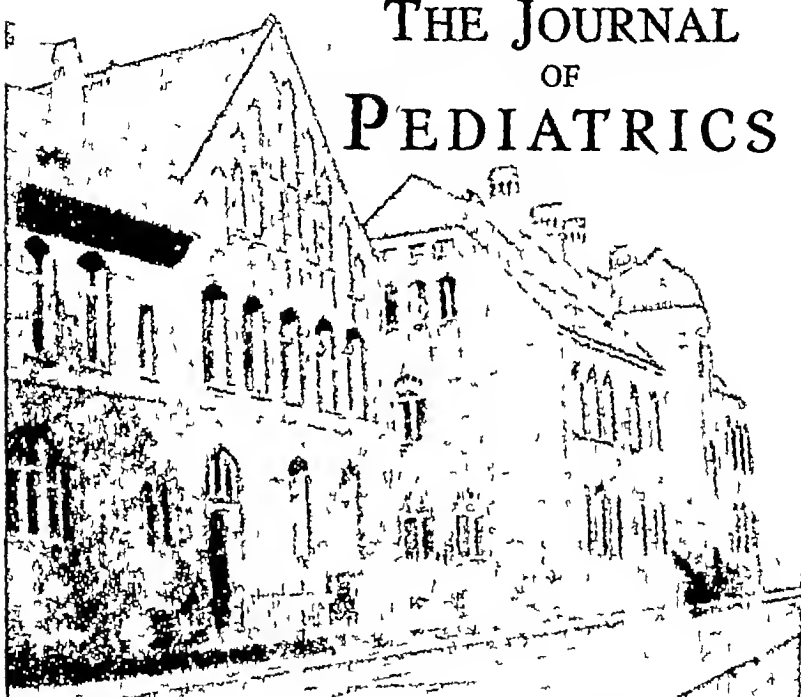
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CZERNY FESTSCHRIFT

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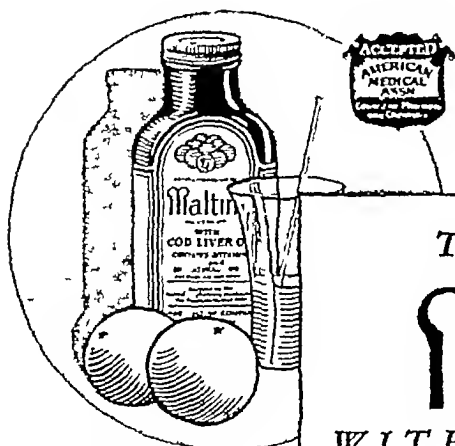
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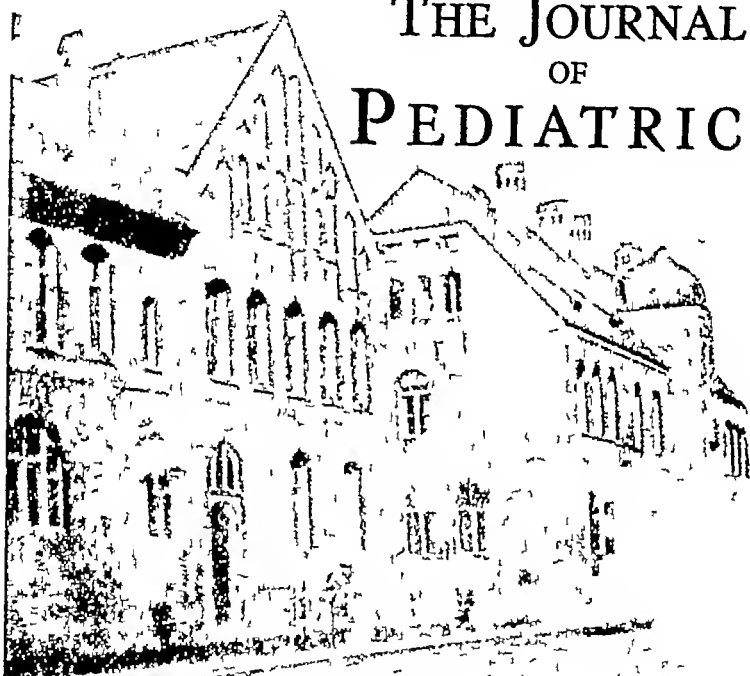
VOL III

JULY 1933

NO 1

CZERNY FESTSCHRIFT

THE JOURNAL OF PEDIATRICS



The University Kinderklinik in Berlin

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of papers

Preventing NUTRITIONAL ANEMIA in Infants through a Normal DIETARY REGIMEN

NUTRITIONAL anemia was present in 45% of the breast-fed and 51% of the bottle-fed in a group of more than 1,000 infants studied by Mackay.¹ Although this anemia was of mild degree, *it was sufficient approximately to double the morbidity among the artificially fed*

Anemia Prevalent

Commenting on this work, the British Advisory Committee on Nutrition writes,

This form of anaemia is prevalent among infants, especially those living under conditions of city life, and is attributed to a deficiency of available iron and possibly also of copper. Its most important feature is susceptibility to infection, particularly a liability to colds, otorrhoea, bronchitis, and enteritis, and a tendency for infections to become chronic.²

Iron, incorporated in powdered milk, should be given as a routine to bottle-fed infants, according to the recommendations of this committee in a report to the Ministry of Health.

Milk Deficient in Iron

Stored in the liver of the full-term infant is a supply of iron and copper theoretically sufficient for the first six months of life. But actually the reserve is subject to wide variation,¹ probably because of variations in the iron content of the mother's diet during pregnancy. Hill, for example, says, "If the mother is anemic herself, or if she has eaten little iron-containing food during the last months of pregnancy, her offspring is born with an insufficient iron deposit."³

	IRON	COPPER
Cow's Milk, 20 oz.	1.44 mg	0.24 mg
Dextri-Maltose with Vitamin B, 1½ oz.	3.60	0.855
Mead's Cereal (dry), ¼ oz.	1.70	0.09
or Pablum	6.74	1.185
Daily Requirement*	4.18	"traces"

When ¼ oz of Pablum is fed to the 3 months-old infant receiving 20 oz cow's milk and 1½ oz Dextri Maltose with Vitamin B, a significant increase in iron and copper takes place.

Containing standardized amounts of this mineral can be administered as early as the third month. Clinical studies by Summerfeldt⁵ show that Mead's Cereal (of which Pablum is the pre-cooked form) is capable of increasing the hemoglobin percentage of growing children.

* The desirable iron intake for children according to Rose *et al.* is 0.76 mg. per 100 calories. Infant of 1 month (8¼ lb.) and infant of 3 months (11¼ lb.) both require 50 calories per lb.⁴

¹⁻³ Bibliography on request.

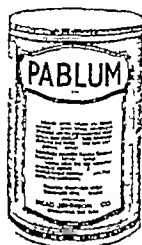
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STIR WITH FORK
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ADD
MILK OR CREAM

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SUPPLIED IN 1 POUND CARTONS AT DRUG STORES

*Pre-cooked Mead's Cereal
Dried Ready to Serve*

Consists of wheatmeal oatmeal cornmeal wheat embryo yeast, alfalfa leaf and beef bone. Supplies vitamins A B E, and G and calcium phosphorus iron, copper and other essential minerals.



Sugar and Salt to Taste for Older Children and Adults

PABULUM is unique among cereals. For it is not only richer than any others in a wider variety of vitamins and minerals but it is the only pre-cooked cereal which is dry-packed yet which can be served hot.

To prepare Pabulum for the infant, all the mother need do is measure the prescribed amount directly into the cereal bowl and add boiled hot water stirring with a fork. (Milk or water-and-milk of any temperature may be used for infants—cream for older children and adults.)

This ease of preparation makes Pabulum especially welcome in families where the benefits of hot cereals are often denied simply because the process of cooking ordinary cereals is too long and too bother

some. As it is a dry cereal, Pabulum keeps indefinitely and requires no refrigeration. Being dry only cereal is paid for not added water. This fact plus the manner in which it is prepared makes Pabulum "economical,—no waste.

Like Mead's Cereal, Pabulum represents a great advance among cereals in that it is richer in minerals (principally calcium, phosphorus, iron, and copper) and vitamins (A, B, E, and G) it is base-forming, and it is non-irritating. Added to these special features it is abundant in protein, fat, carbohydrates and calories.

Unlike many foods that are "good for growing children," Pabulum *tastes* good.

MEAD JOHNSON & CO, Evansville, Indiana, Pioneers in Vitamin Research

Please enclose professional card when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons

HAVE YOU SEEN Clapp's NEW Enamel Purity Pack?

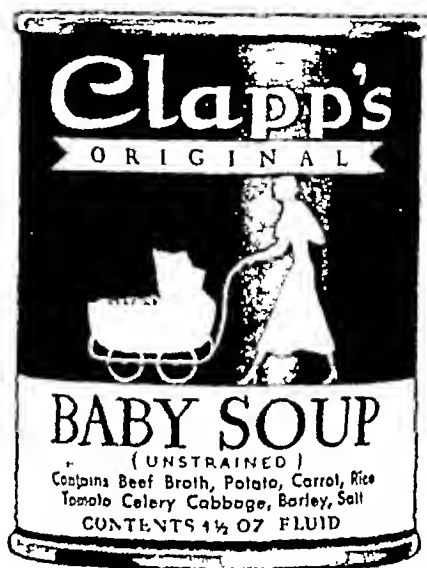
CLAPP'S Original Baby Soups and Vegetables are now being sold all over the country in the new Enamel Purity Pack and sold at a new low price

These metal containers afford a special enameled protection against food acids. They provide the purest packing that baby foods can receive!

America's largest variety of infant foods can now be purchased as cheaply as any other reputable brand in the field. So if, in the past, you have wished to give your young charges Clapp quality but have hesitated because of a slightly higher price you can now freely advise these favorite foods

We want you to see and try Clapp's foods in their new packing. Send in the coupon and receive them all—free.

Clapp's original Baby Soups and Vegetables • • also packed in glass jars at former prices



• 15 VARIETIES •

Baby Soup (Strained)	Baby Soup (Unstrained)
Vegetable Soup	Beef Broth
Wheatheart Cereal	Spinach
Carrots	Peas
Tomatoes	Asparagus
Beans	Beets
Prune Pulp	Wax
Apple Sauce	Apricot



HAROLD H. CLAPP, INC.
Dept. J-4, 1328 University Ave.
Rochester, N. Y.

Please send me free of charge a complete assortment—15 varieties—of Clapp's Original Baby Soups and Vegetables in the new Enamel Purity Pack.

Name _____

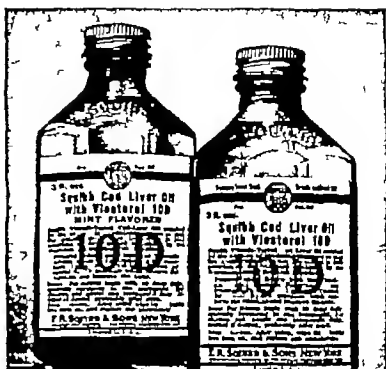
Address _____

City _____ State _____

Please print name and address plainly



Keep babies on
cod-liver oil
this summer!



Most physicians now recognize the need for prescribing an anti rachitic *all year round*, in summer as well as during the more inclement seasons. Comparatively few babies they find receive enough Vitamin D from sunshine even when the weather is warm.

There is the danger with very young babies of exposing them too long to the sun the risk with babies in large cities that other factors such as smoke and soot may prevent them from receiving some of the sun's protective rays and the possibility that bad weather may make outdoor protection uncertain and irregular.

This is why it is desirable in summer to depend on some regular daily source of Vitamin D. Many doctors prescribe Squibb 10D Oil. Specially enriched with Viosterol it has *ten times* the Vitamin D potency of standard cod liver oil as defined by the

Wisconsin Alumni Research Foundation.

Babies tolerate it easily. There is very little danger of digestive upset. One tea spoonful of cod liver oil supplies only about 40 calories.

In addition to Vitamin D Squibb Cod Liver Oil with Viosterol 10D contains an abundance of Vitamin A, the factor which promotes growth and is an aid in building resistance. Many physicians favor giving babies plenty of Vitamin A in summer to help acquire good general resistance with which to meet infections.

Every 100 grams of Squibb 10D Oil contains not less than 70,000 U.S.P. units of Vitamin A and 133,333 A.D.M.A. (13,333 Steenbock) units of Vitamin D.

Babies need these factors at any season. Prescribe Squibb Cod Liver Oil with Viosterol 10D for them routinely all summer.

SQUIBB COD-LIVER OIL
with **VIOSTEROL**

PLAIN OR MINT FLAVORED

10D

Manufactured under license from the Wisconsin Alumni Research Foundation and accepted by the Council on Pharmacy and Chemistry, A. A.

ELI LILLY AND COMPANY

FOUNDED 1876

Makers of Medicinal Products

AMPOULES PHYSIOLOGICAL BUFFER SALTS

(Hartmann's Solution)

For the Treatment of Dehydration with Acidosis or Alkalosis

Supplied through the drug trade in 10 cc ampoules, No 261, and in 20 cc ampoules, No 262 each in boxes of six and twenty-five ampoules

AMPOULES MOLAR SODIUM R-LACTATE

Prepared according to the method of Dr Alexis F Hartmann

For the Treatment of Severe Acidosis When Prompt Action
Is Necessary

Supplied through the drug trade in ampoules containing 40 cc, No 278, in boxes of a single ampoule, and in boxes containing six and twenty-five ampoules

PROMPT ATTENTION GIVEN TO PHYSICIANS' INQUIRIES

ADDRESS ELI LILLY AND COMPANY, INDIANAPOLIS, INDIANA, U S A



VEGEX

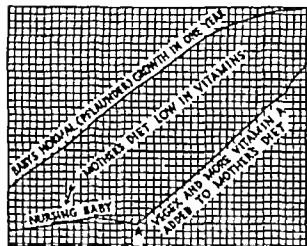
for the B Vitamins B₁-B₂ or G

VegeX—How Made

VegeX comes from barley and corn slow grown brewers yeast. After settling from the beer the hop resins are washed out, a small amount of salt added and autolyzed or digested by the enzymes in the presence of the salt. The extract is filtered off, condensed and a small amount of flavoring from such vegetables as tomato and celery added. Insignificant to chemical composition or vitamin B potency.

The finished condensed extract contains around 11 per cent of sodium chloride which figures less than a gram per teaspoonful in arranging diets. The iron, contained in the whole grain is gathered by the yeast and is particularly available in VegeX.

Constant Feeding Tests for Vitamin B Strength



The vitamin B potency of VegeX is checked constantly by feeding tests not only for the unit required for recovery after depletion but the amount required for good normal growth successful reproduction and successful rearing.

From 50 to 100 mg give recovery after depletion. 200 mg give normal growth, 400 to 600 mg give successful rearing of young. On these standards VegeX ranks at the top.

Early Use for Vitamin B

When Funk discovered the thing he named "Vitamin B" the VegeX extract was found a potent, palatable and available food source was selected during the World War to prevent and relieve beriberi among the troops in Germany to add protein to the restricted food supply.

After the war VegeX was early turned to in medical centers as a source of vitamin B₁ later of B₂ or G. The pronounced value of VegeX for stimulating appetite, increasing milk consumption and aiding growth among both nursing and bottle-fed babies for promoting lactation for the mother and in gastrointestinal and related disorders has been shown.

It may stimulate finicky or capricious appetites. Is of value in the liquid diets for post-operative cases. It aids increased consumption of food. Is frequently a means for quick pick up in strength.

In Anemias

Medical centers in India, Porto Rico, England and the United States report the value of this vitamin B extract sold in England as Marmite and in the United States as VegeX in the treatment of pernicious and related anemias. Wills (British Medical Journal, June 7, 1931), Vaughan and Hunter (The Lancet, April 16, 1932), Goodall (The Lancet, Oct. 3, 1932), Strunz and Castle (The Lancet, July 16, 1932), Ungley (The Lancet, Oct. 15, 1932), Reiterer Wills Camb and Lomel report in the Lancet (June 1, 1933).

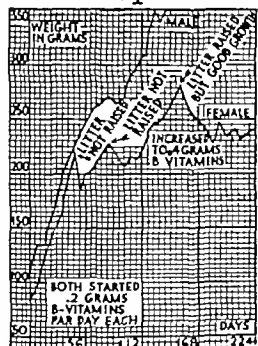
1. Clinical trial of rous preparations containing vitamins B₁ and B₂ failed to show that any of these vitamins has haemopoietic properties in tropical macrocytic anemia.

2. Marmite (VegeX, the United States) an autolyzed yeast product was act curatively in similar cases.

Chart No. 1 on this page shows the amount of B vitamins necessary for successful rearing as compared with the amount one-half which gives good growth.

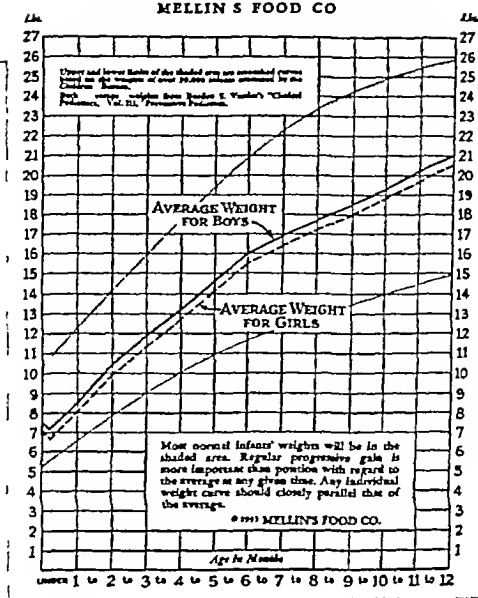
Chart No. 2 shows an increase in growth when the mother's diet is supplemented with the A and B vitamins. To the vitamin C should have been added.

Sufficient samples for clinical use, and "VITAMINS," book brings the subject up to date together with special directions for the use of VegeX by physicians sent on request.



VITAMIN FOOD CO, INC and VEGEX INCORPORATED
122 HUDSON STREET NEW YORK CITY

PREPARED FOR THE USE OF PHYSICIANS BY
MELLIN'S FOOD CO



May We SEND YOU THIS NORMAL
GROWTH CHART?

In keeping with our
policy—*no advertising or feeding formulas
for the public*—this new chart will be dis-
tributed upon request to physicians only.

MELLIN'S FOOD CO
Boston, Mass

No
ADVERTISING
or feeding formulas
for the public.

EXPLOITATION *of the* MEDICAL PROFESSION

EVERYWHERE it is rampant — newspapers, magazines, billboards, radio
 "Your doctor will tell you that " "Medical science has found that
 "The greatest specialists in Timbuctoo say that " And the
 rest of the story is, of course, "Use our pills or our vitamins three times
 a day; ask your doctor "
 ♦ ♦ ♦

You are forced to compete with those who offer your patients free ad
 vice regarding medical treatment. You deliver Mrs Blank's baby today,
 and tomorrow she will receive by mail samples of baby foods with com-
 plete directions how to use them. Indeed, some physician representing a
 commercial organization and knowing that the case is in your hands may
 address a personal letter to your patient offering his services free
 ♦ ♦ ♦

It has been said that ten more years of the present trend of interference
 in medical practice will do away with the need for private practice of
 infant feeding and other branches of medicine
 ♦ ♦ ♦

Mead Johnson & Company have always believed that the feeding and
 care of babies and growing children is an individual problem that can
 best be controlled by the individual physician. For over twenty years and
 in dozens of ethical ways we have given practical effect to this creed.
 We hold the interest of the medical profession higher than our own, for
 we too, no doubt, could sell more of our products were we to advertise
 them directly to the public.
 ♦ ♦ ♦

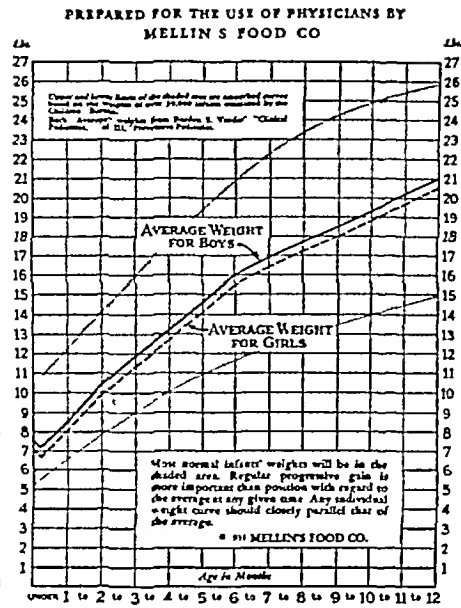
So long as medical men tacitly encourage the present trend, so long will
 serious inroads continue to be made into private medical practice. When
 more physicians specify MEAD'S Products* when indicated, more
 babies will be fed by physicians because Mead Johnson & Company
 earnestly cooperate with the medical profession along strictly ethical
 lines and never exploit the medical profession.

★ Dextri Maltose Nos. 1, 2 and 3; Dextri Maltose with
 Vitamin B; Mead's Viosterol in Oil 250 D; Mead's
 10 D Cod Liver Oil; Mead's Newfoundland Cod Liver Oil;
 Mead's Cereal; Mead's Brewers Yeast Powder; Mead's
 Brewers Yeast Tablets; Mead's Powdered Lactic Acid
 Milk Nos. 1 and 2; Mead's Powdered Whole Milk
 Alacta; Mead's Powdered Protein Milk; Casec; Recolac
 Sobee; Mead's Viosterol in Halibut Liver Oil 250 D;
 Mead's Undiluted Halibut Liver Oil



"We Are Keeping the Faith"

Please enclose professional card when requesting samples of Mead Johnson products in cooperation in preventing their reaching unauthorized persons.

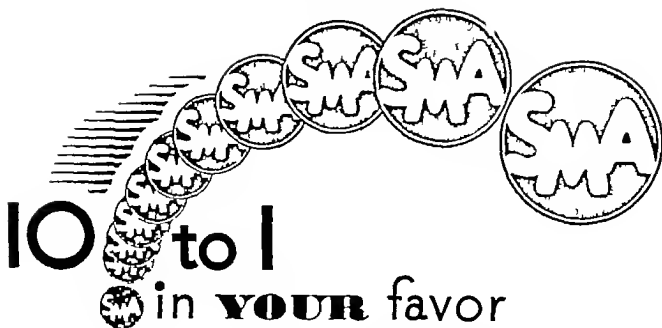


May We SEND YOU THIS NORMAL
GROWTH CHART?

In keeping with our
policy—*no advertising or feeding formulas
for the public*—this new chart will be dis-
tributed upon request to physicians only.

MELLIN'S FOOD CO
Boston, Mass

No
ADVERTISING
or feeding formulas
for the public.



WHEN you prescribe S.M.A. for a normal infant deprived of breast milk you do so with the assurance that the chances are 10 to 1 that the child will do unusually well on it.

S.M.A. produces excellent nutritional results in most cases and produces these results more simply and more quickly and there is a wealth of clinical evidence to back that claim.

Physicians Report Results

As one example of this, take the following answers to a questionnaire sent to a representative group of physicians early in our work:

Q.—Have the average results obtained by you in feeding S.M.A. been excellent, good, fair or poor?

A.—Excellent 74.2%
Good 25.8%
Fair 0%
Poor 0%

Q.—Do you feel that S.M.A. is of value to you in your practice from the stand point of preventing nutritional diseases?

A.—Yes 97.1%
Undecided 2.9%

Q.—Has the feeding with S.M.A. been easier and less annoying than with other foods or mixtures used by you heretofore?

A.—Yes 100%

Q.—Have your nutritional results been better than with other foods or mixtures used by you heretofore?

A.—Yes 83%
No 14.6%
Undecided 2.4%

If you are interested in saving yourself exacting detail in infant feeding, and want to be assured of excellent results in most cases you can do no better than prescribe S.M.A., the formula prepared with laboratory exactness for infants deprived of breast milk.

S M A Ahead in 1915 Still Far Ahead

S.M.A. has been antrachitic from its beginning in 1915. S. M. A. was a revolutionary departure then, was far ahead in 1921 when it was offered to the profession generally and is still far ahead in numerous unheralded ways some of which are:

1. Buffer value is practically identical with breast milk.
2. Fat has the same Reichert-Meissl number, Iodine number, Polenske number, Saponification number, melting point and refractive index as breast milk fat.
3. The pH is the same as breast milk.
4. Electrical conductivity is the same as breast milk.
5. Freezing point is the same as breast milk.
6. Osmotic pressure is the same as breast milk.
7. Curds produced by the action of the gastric juices on S.M.A. are soft and practically the same as breast milk.
8. Stools are acid and also physically similar to those of breast fed infants.

S M A Is The Only Antirachitic Breast Milk Adaptation



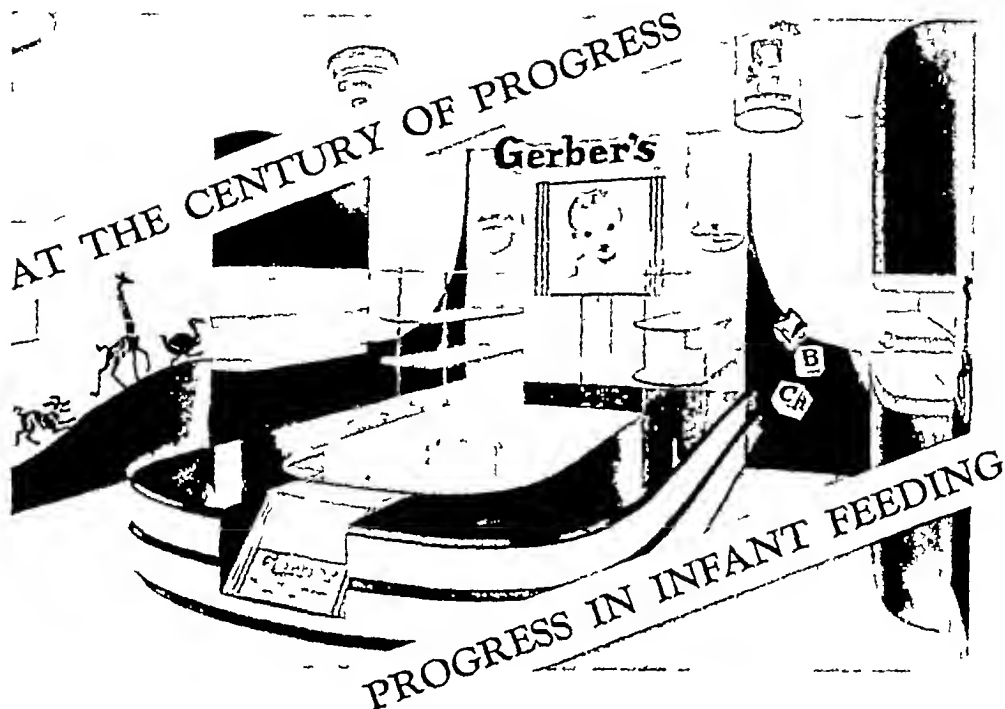
S.M.A. is a food for infants—derived from tubercular tested cows' milk, the fat of which is replaced by animal and vegetable fats including biologically tested cod liver oil; with the addition of milk sugar, potassium chloride and salts; altogether forming an antirachitic food. When diluted according to directions, it is essentially similar to human milk in percentages of protein, fat, carbohydrates and ash in chemical constants of the fat and in physical properties.



Try S.M.A. in your own practice. For samples simply attach this paragraph to your letterhead. S. M. A. Corporation, 4614 Prospect Ave., Cleveland, O.

55-73

S M A PRODUCES RESULTS MORE SIMPLY AND MORE QUICKLY



THE many professional requests for samples of Gerber's Strained Foods are indicative of the physician's interest in the commercial developments required to keep pace with medical progress in infant feeding.

The Gerber Products Company welcomes and invites this continued interest. May we urge you cordially to visit the Gerber Exhibit at the Century of Progress Exposition and learn at first hand about the Gerber Strained Products for Baby?

Mr. R. W. Decker and Mr. Walter Fleming, who have specialized on Gerber detail work with physicians, will be in charge of the exhibit.

They will be assisted by Miss Harriet E. Davis, R. N.—for the past 9 years Director of the College of Nursing at Indiana State University and just recently associated with the Gerber Department of

Nutrition directed by Lillian B. Storms, Ph. D.

Miss Davis is particularly well qualified thru her professional work and training to impress on lay visitors the importance of relying only on a physician's advice on all questions connected with infant feeding. This Gerber policy of active co-operation with the medical fraternity maintained in all Gerber advertising will be followed rigidly in lay contacts at the Century of Progress.

The Gerber Exhibit is located in the Hall of Science Fountain Rotunda, Century of Progress Exposition. You are invited to use its convenient location as a meeting place.

GERBER PRODUCTS COMPANY
Fremont, Michigan

(In Canada: Fine Foods of Canada
Ltd., Windsor, Ont.)



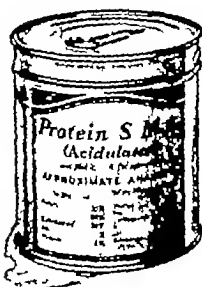
Gerber's

9 STRAINED FOODS FOR BABY

STRAINED Tomatoes—Green Beans—Beets—Vegetable Soup—Carrots—Prunes—Peas—Spinach, 4 1/2 oz. cans.

STRAINED Cereal, 10 1/4 oz. cans
15c at Grocers and Druggists

A Worthy Companion Product to S M. A.



PROTEIN S.M.A. (ACIDULATED)

Analysis*

Protein	3.5%	Ash	0.6%
Fat	2.2%	pH	4.6
Carbohydrate	2.8%	Calories per ounce	15
		Calories per 100 c.c.	50

* When diluted according to directions

S M A. is for normal infants. Protein S.M.A. (Acidulated) was developed to suit certain deviations from normal. It has been used by physicians for years with satisfactory results.

Uses of Protein S M A. (Acidulated)

- For the correction of diarrhea, malnutrition and marasmus
- For prematures and other infants requiring a high protein intake
- May be used either as a protein milk or as a lactic acid milk.

Characteristics of Protein S M A. (Acidulated)

A cultured lactic acid food for prematures and other infants requiring a high protein intake for the correction of diarrhea, malnutrition and marasmus derived from tuberculin tested cows' milk the fat of which is replaced by animal and vegetable fats including biologically tested cod liver oil with the addition of lemon juice, casein potassium chloride and salts altogether forming an *antirachitic* and *antiscorbutic* food. ○...

How to Correct Diarrhea

After a starvation period of twelve to twenty four hours on boiled water or gelatin water (½ ounce of gelatin to one pint of boiled water) the infant should be given according to the following schedule Protein S. M. A. (Acidulated) prepared in proportion of four level tablespoons to nine ounces of water:

	1st Day	2nd Day	3rd Day
Severe cases	3 oz.	6 oz.	9 oz.
Medium cases	10 oz.	15 oz.	20 oz.
Mild cases	15 oz.	30 oz.	

The above quantities are to be increased until the proper amount for the patient's age and condition is reached, which is 200 c.c. per kilo of body weight per twenty four hours, or three ounces per pound of body weight per twenty four hours. However the total twenty four hour intake need not go above thirty two to thirty five ounces or 960 to 1050 c.c.

After 48 hours, or sooner if the diarrhea has stopped, ALERDEX (Protein Free Maltose and Dextrins) should be added *gradually* beginning with one ounce to the quart, and increasing until the infant is gaining steadily in weight. In certain cases it may be necessary to increase the carbohydrate to a total of 12 to 15% (3 to 4 ounces of carbohydrate to the quart).

SEND FOR LITERATURE

Simply attach this paragraph to professional card or letterhead for literature on Protein S M A. (Acidulated). 56-73

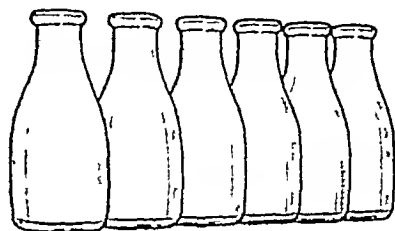


**S M A.
CORPORATION
CLEVELAND OHIO**



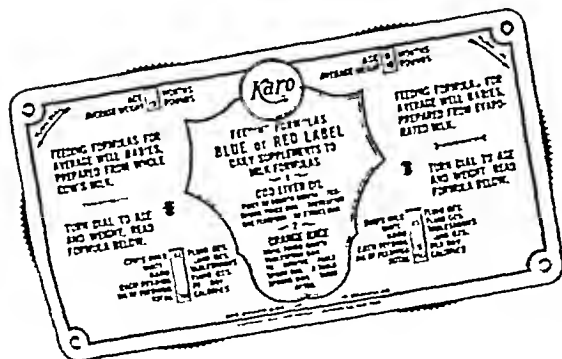
ONE inexpensive can of KARO SYRUP effectively modifies SIX quarts of whole milk

ON THE basis of tested and approved feeding schedules averaged for babies up to an age of nine months, one tablespoon of Karo would be used with about 6 fluid ounces of milk. On this basis, a one and one half pound tin of Karo (which sells in grocery stores for about 12¢) will furnish the necessary amounts of easily assimilated carbohydrates, dextrin, maltose and dextrose, for 6 quarts of whole milk. Probably no other infant food of equal acceptance is available at such low cost as Karo.



Feeding schedules, are not supplied to the laity. Mothers are always advised to consult a physician in regard to the nutritive requirements of the infant.

Use of the pouring spout (furnished without charge) is recommended. This spout insures cleanliness—lessens danger of contamination—prevents waste.



FREE TO PHYSICIANS

This convenient calculator of feeding schedules is accurate, instructive and helpful. The makers of Karo will gladly send one to you on receipt of your name and address. Write to Corn Products Refining Company, 17 Battery Place, New York City.



RAPIDLY GAINING FAVOR

**ALERDEX - THE PROTEIN-FREE
MALTOSE AND DEXTRINS**

WHY IS ALERDEX PROTEIN-FREE?

• Since certain proteins are frequently the cause of eczemas and other forms of allergy, it is desirable to eliminate these offending proteins from the infant diet. Cereal proteins are frequently present as contaminants in some milk modifiers. The routine use of a protein free carbohydrate in all milk modifications should help to diminish the incidence of these troublesome eczemas. Alerdex is a protein free carbohydrate developed by our Research Division to meet this need and the demand for it is steadily increasing.

A modest announcement of Alerdex a year ago found physicians ready and anxious for such a product. There is now a definite trend to use Alerdex routinely in all milk formulas.

Of course Alerdex should always be used as the carbohydrate addition with Smaco Hypo Allergic Milks with the assurance that eczemas due to cereal protein sensitization will not be aggravated.

CHARACTERISTICS OF ALERDEX

- 1 Helps prevent eczemas when used routinely due to absence of offending protein.
- 2 Use present formulas because Alerdex has same caloric value and percentage of maltose and dextrins.
- 3 Does not cake on exposure to air because it is non hygroscopic.
4. Dissolves readily in warm water or milk.
- 5 Snow white, free flowing powder
- 6 Inexpensive—in spite of extra processing under technical control, costs no more

APPROXIMATE ANALYSIS OF ALERDEX

Alerdex is essentially a mixture of approximately equal parts of maltose and dextrins. It is prepared by a new thermally-controlled process of the enzyme hydrolysis of non cereal starch, as a result of which it contains no protein contaminant.

Moisture	3.0
Ash	0.5
Fat (ether extract)	0.0
Hydrolyzed protein (N x 6.25)	0.5
Reducing sugars as maltose	50.0
Dextrins (by difference)	45.0
Level tablespoons, per ounce	4
Calories per level tablespoon	27½
Calories, per ounce	110



Prescribe Alerdex in your own practice. For samples and literature simply attach this paragraph to your letterhead or prescription blank. S.M.A. Corporation, 4814 Prospect Avenue, Cleveland, Ohio 66-73

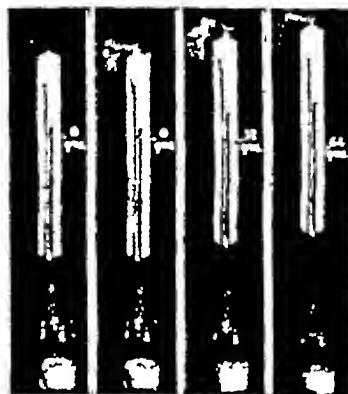
© 1952, S.M.A. Corporation, Cleveland, Ohio

PRESCRIBE ALERDEX THE PROTEIN-FREE MALTOSE AND DEXTRINS

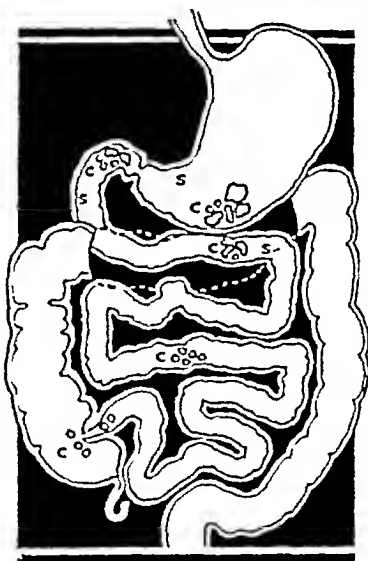
CURD TENSION

- AND INFANT FEEDING -

ITS • EFFECT • UPON • THE • ASSIMILATION • OF
PROTEINS



BREAST MILK SIMILAC POWDERED MILK COW'S MILK



C—Cow's milk S—Similac
Schematic drawing of the relative size of the curds of cow's milk and Similac vomited by six weeks old puppies after one-half hours ingestion.

"THE most available and the most easily digestible form of protein for infants is the protein of milk. The protein of breast milk is more digestible than that of cow's milk."

"In the light of our present knowledge, the chief cause of the difference in the digestibility of the protein of human milk and that of cow's milk lies in the greater proportion of casein in cow's milk."

"It is the formation of large curds which renders the casein of cow's milk so much more difficult of digestion by the infant than that of human milk. If the formation of large casein curds in the stomach can be prevented, the casein of cow's milk is easily digested."

In SIMILAC the large casein curds are not formed. The curds formed when the gastric enzymes act upon SIMILAC are small and flocculent, registering zero on the tensiometer, as shown in the illustration, hence more easily digested.

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes. Result—a more complete utilization of the food elements.

*Morse and Talbot: Diseases of Nutrition and Infant Feeding, pg. 214, 215

Samples and literature will be sent on receipt of your prescription blank.

SIMILAC—Made from fresh skim milk (casein modified) with added lactose, salts, milk fat and vegetable and cod liver oils.



M & R
DIETETIC LABORATORIES, INC.,
COLUMBUS, OHIO.

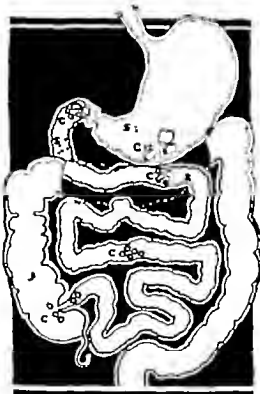
CURD TENSION

- AND INFANT FEEDING -

ITS EFFECT UPON THE ASSIMILATION OF SALTS



BREAST MILK SIMILAC POWDERED MILK COW'S MILK



C—Cow milk S—Stool
Schematic drawing of the relative size of the curds of cow's milk and Similac vomited by six weeks old puppies after one-half hour ingestion.

THE mineral salts play a very complicated part in digestion because they are not only absorbed by the intestines but also may be re-excreted into the digestive canal.¹

"The mineral salts are of even greater importance in infancy than in later life because of the rapid growth of the bony structure. The salts are also necessary for cell growth and are important constituents of the blood and digestive juices, facilitating secretion, absorption and excretion."²

Some of the important mineral salts are encased within the large tough curds formed from cow's milk, and only those salts that are not encased in the curds are available for metabolism.

The curds formed from SIMILAC are small and flocculent, registering zero on the tensiometer as shown in illustration hence the mineral salts of SIMILAC are available for metabolism.

The salts of the cow's milk used in the preparation of SIMILAC are rearranged, particularly with reference to calcium, sodium, and potassium, as well as phosphorus and chlorine. SIMILAC has a salt balance that cannot be obtained in the ordinary milk dilutions or modifications as made in the home or laboratory.

The finer the curd the greater the surface area. The greater the surface area the more exposed are the fats, carbohydrates, proteins and salts to the digestive enzymes. Result—a more complete utilization of the food elements.

¹ Hersh and T. H. Diseases of Nutrition and Infant Feeding, pg. 59

² M. H. Infant Nutrition, pg. 43

Samples and literature
will be sent on receipt of
your prescription blank.

SIMILAC—Made from fresh skim milk (cream removed); with added lactose, salts, milk fat and egg yolk and cod liver oils.



M & R
DIETETIC LABORATORIES, INC.,
COLUMBUS, OHIO.

Effective LAXATIVE MEDICATION

Sodium Glycocholate..... $\frac{1}{4}$ gr
Sodium Taurocholate..... $\frac{1}{4}$ gr
Phenolphthalein..... $\frac{1}{2}$ gr
Extract Cascara..... $\frac{1}{2}$ gr
Aloin..... $\frac{1}{8}$ gr

TABLETS

OXIPHEN



Oxiphen Tablets are particularly useful in habitual constipation because they produce gentle, yet effective laxative action throughout the intestinal tract, stimulating activity of both the secretory organs and the intestinal musculature. They may be used over extended periods without losing their

effect, and without an increase in dosage and, as normal function is re-established, the dosage may be gradually withdrawn without a return of the condition. The formula contains no toxic drugs, and does not produce the "cathartic habit."

The Oxiphen formula combines the hepatic stimulant and chologogue action of the bile salts ("the only reliable chologogue known"—Cushny) with the tonic laxative effect of cascara, the simple laxative action of phenolphthalein and the stimulant action of aloin on the colon. Kindly use the coupon for literature and clinical sample.

PITMAN-MOORE COMPANY

Indianapolis

PITMAN MOORE COMPANY, Indianapolis

You may send me a sample of Oxiphen Tablets for clinical use

M.D.

Address _____

City _____

State _____

YOUR FORMULA with bridge table variations



"Be sure to use
That's what I use



"My mother always says
— is best for a baby



"Try — Brand It's such
a pretty name for a milk, isn't it?

MUCH free advice on infant feeding can be obtained across the bridge table. But should a mother rely upon this kind of advice to guide her in her choice of Evaporated Milk for baby?

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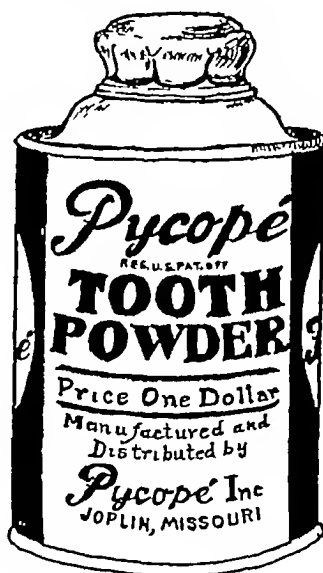


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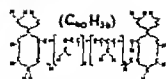
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[References Available—A digest of the literature dealing with carotene and vitamin A deficiency diseases, reprinted from American Medical Journals, available to physicians on request. 73 references are included.]



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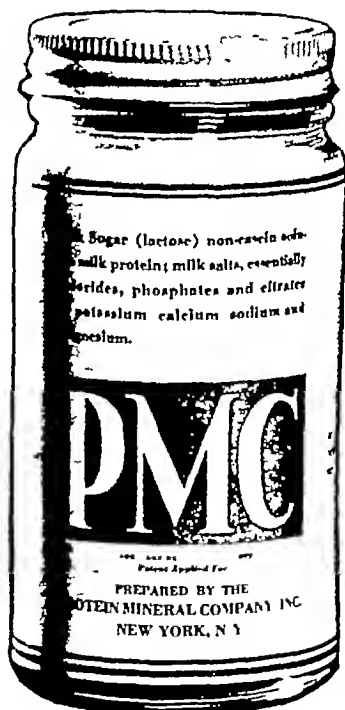
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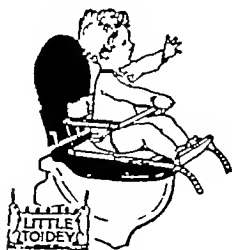
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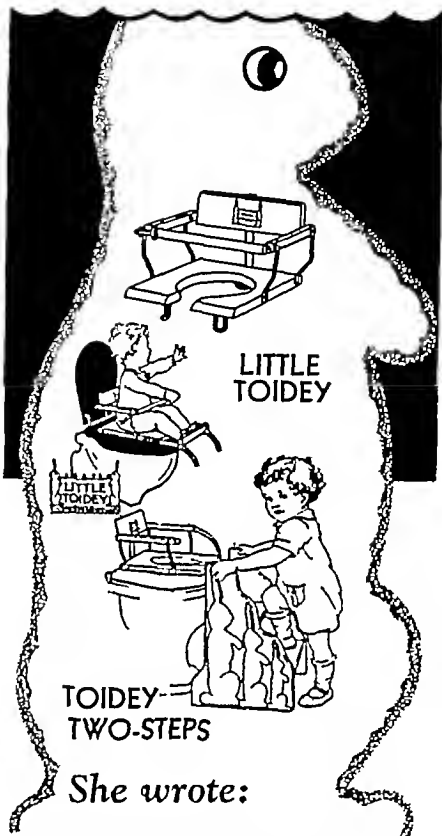


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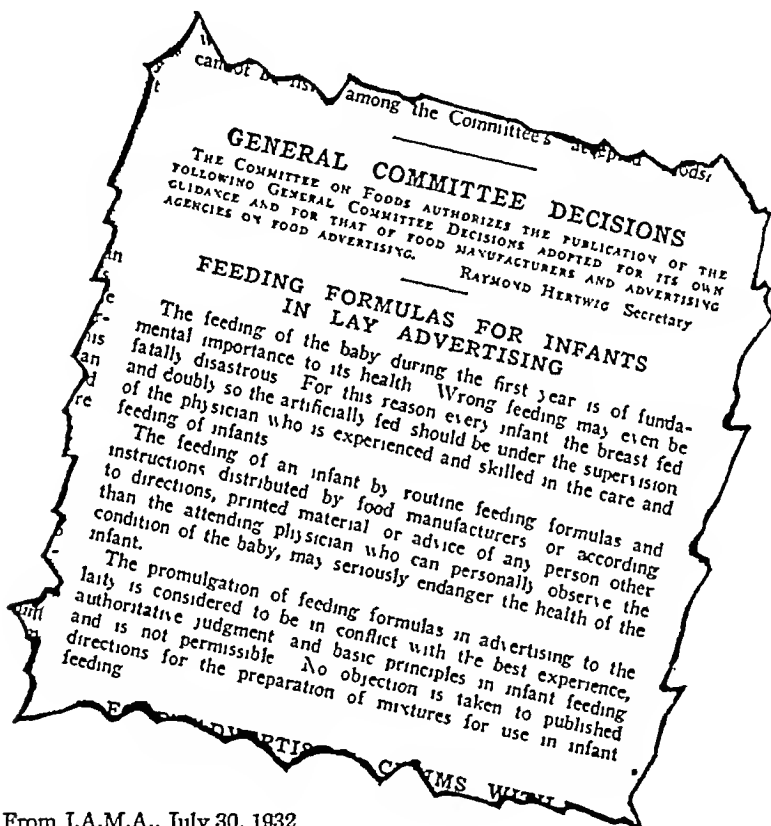
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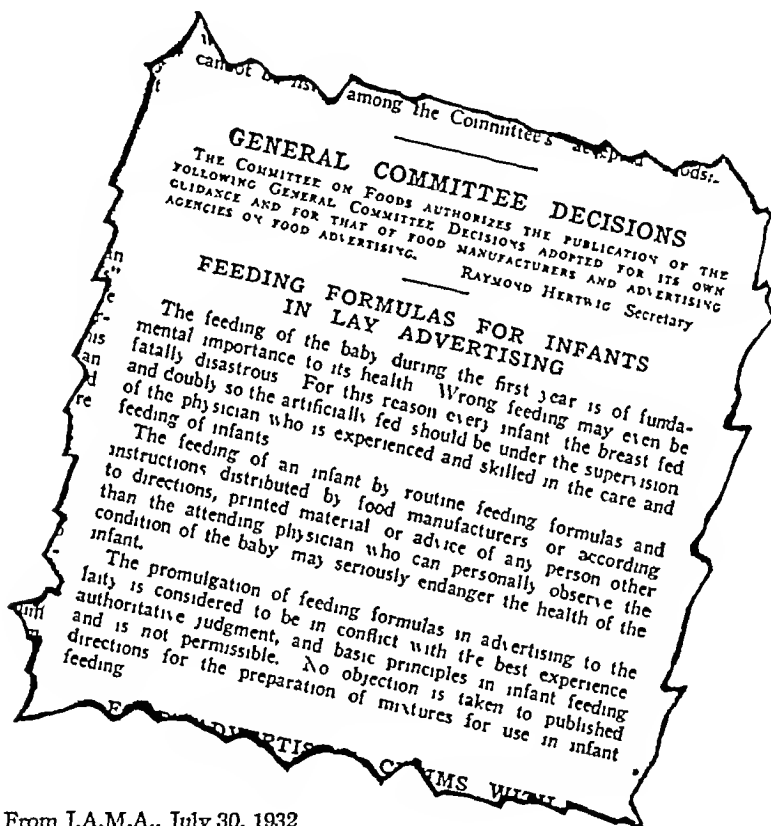
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ADALBERT CZERNY—AN APPRECIATION

THE publication of this Festschrift by an American journal of *pediatrics* is evidence of the high esteem in which Adalbert Czerny is held and the appreciation that American pediatrics has for his contributions to the care of the sick and of the well child. To some of us who had the privilege of working with Professor Czerny during the Breslau days, it seemed inevitable that he should be chosen to fill more important positions as they became available.

Graduating from the German University of Prague in 1888, he became a privat dozent in Professor Epstein's Clinic in Prague in 1893 and in the following year was called to Breslau as Professor of Pediatrics to succeed Doctor Soltmann. In a remodelled flat, the polyclinic was opened in 1894 and shortly afterward an adjacent building was remodelled and served as a clinic for several years. In 1901 the new clinic was opened and in its arrangement Professor Czerny emphasized for the first time the value and importance of carefully observed dispensary material for the development of the hospital and its importance for the instruction of students and practitioners.

Some very interesting studies resulted from the careful observations made in this polyclinic. The clinic, with its convenient laboratory and library, was a place in which it was a pleasure to work. The daily rounds at 12 o'clock frequently lasted until late into the afternoon as a particular case of interest was discussed in great detail in the masterful manner of the Professor. It was quite an international family that gathered together at the Kinderklinik and I recall many interesting and happy days there. In 1910 Professor Czerny was called to Strassburg to take over the newly built Children's Clinic. It was during his first year in Strassburg that Doctor John Howland spent many months working in his clinic and derived much inspiration for the development of the pediatric clinic at Johns Hopkins. The Strassburg Clinic was a wonderful complex of buildings that Czerny was to leave after three years to accept the foremost pediatric chair in Germany which was

vacated by Professor Huebner in 1913. At the old Charite Kinderklinik, the chair of pediatrics occupied in succession by Professors Henoch, Huebner and Czerny is to the German pediatrician the highest honor that can be achieved. Although handicapped by old buildings and with insufficient funds to rebuild after the World War, the wealth of material and the intensity of work made the clinic a Mecca for graduate students. Having had the opportunity to visit Czerny's clinics in all three cities, I could not help but appreciate how fortunate I had been to have spent my student days with him in Breslau where, in a small group, an intimacy existed impossible at the larger clinics. Profoundly independent in all of his ideas, he combined the rare abilities of a great clinician, of an ardent teacher, and of a keen research worker. Professor Czerny is an excellent musician and plays the cello unusually well. The musical evenings in his home are a most delightful memory. His hobby is photography.

Professor Czerny's contributions show his manifold interests. His early work on sleep, on amyloidosis and on blood volume are a prelude to his greatest contributions, namely, his work on the gastrointestinal diseases of infancy. His first publication was with Moser, appearing in 1894, from Epstein's Clinic in Prague. His interest did not restrict itself to the diseases of the gastrointestinal tract but grew until it encompassed the nutrition of the normal infant and child in all its phases, as well as a comprehensive study of the nutritional disturbances of childhood. The culmination of his work and that of his many students, together with a complete study of the subjects, is the monumental work written with Keller, "Des Kindes Ernährung und Ernährungsstörungen und Ernährungstherapie." The first edition appeared in 1906 and the following year, and a second edition in 1925-1927. To the student of child nutrition this work is a bible.

There is another book to which I want to refer because it represents Czerny at his best. At a time when a very few were thinking of the relation of the pediatrician to the education of normal and difficult children, Czerny published his little book "Der Arzt als Erzieher des Kindes." Thus anticipated by many years our efforts to treat the behavior disturbances of children. Appearing in 1908, it has gone through seven editions and is as useful today as it was when first published.

In conclusion, let me state again that in honoring Professor Czerny on his seventieth birthday we are but repaying a debt that American pediatricians owe to him and to many others in Germany. At a time when pediatrics in America was still in its swaddling clothes, German masters took us into their clinics as students and by their inspiration and training played a part in the development of pediatrics in America of which they may well feel proud.

HENRY F. HELMHOLTZ

ERYTHROBLASTOSIS IN ICTERUS GRAVIS NEONATORUM

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INTRODUCTION

GRAT advances have been made in the past few years in our knowledge of the growth and development of the hematopoietic system. One of the greatest gaps in our knowledge of the physiology of hematopoiesis concerns the vital changes which take place just preceding and following birth. The differences in habitat between the intrauterine surroundings of the fetus, and the extrauterine environment of the infant, require different physical and chemical physiologic responses from fetus and infant, as has been shown by Czerny.¹ The intrauterine and extrauterine physiology of respiration and circulation are probably better understood than the corresponding physiology of the hematopoietic system.

The embryology and development of the hematopoietic system is fairly definitely known and extramedullary blood formation is a fetal characteristic. The embryonic blood contains some elements (primitive erythrocytes) which are not encountered in the extrauterine circulation. There is still insufficient knowledge as to the fetal deposition of iron in the organs of the body. Bunge's theory of an iron reservoir or depot laid down in the liver in the last few months of fetal life which has so long been an accepted explanation is no longer held.

Following the onset of labor a gradual and continuous destruction of the erythrocytes of the polycythemic fetal blood occurs for a varying period. The exact site of this blood destruction is thought to be in the cells of the reticuloendothelial system and also to occur directly in the blood stream. Certainly according to Mann and his coworkers²⁰ the conversion of hemoglobin into bilirubin, does not occur in the liver cells. Physiologic icterus neonatorum is closely linked with this destruction of the polycythemic blood of the newborn.

Under the title *icterus gravis neonatorum* a group of cases reported in the literature have been segregated into a definite clinical syndrome. Newborn infants either at birth or a few hours thereafter develop a rapidly deepening jaundice associated with anemia and the presence of a great number of immature red blood cells, erythroblasts in the circulation. Associated with the jaundice, anemia and erythroblastic blood picture are Kern icterus, iron deposition in

the internal organs, extensive extramedullary foci of blood formation, familial history, sometimes enlargement of the placenta and yellow coloring of the vernix caseosa, and infrequently a slight edema

An elucidation of the etiology of this disease of the newborn, would no doubt throw great light upon the physiology of hematopoiesis in the newborn and upon the mechanism of physiologic icterus neonatorum. Some very recent reports have suggested the association of familial icterus gravis with other diseases of the newborn. They may be grouped as follows:

(A) Icterus gravis neonatorum has been closely linked with hydrops congenitus universalis.^{2, 11} (B) Most recently it has been suggested that the clinical entity termed "anemia of the newborn" may show characteristics relating it to both icterus gravis neonatorum and hydrops congenitus.^{10, 11, 12, 41, 45} (C) Since the comprehensive review by Knoepfelmacher¹³ in 1910, infection has been suggested as the etiologic agent, causative of icterus gravis neonatorum, and two recent reports suggest such an etiology.^{14, 15} I wish to add two cases of icterus gravis neonatorum with erythroblastosis to those already reported and to present a speculative discussion on the pathologic relationships of this clinical group.

CASE REPORTS

CASE I.—Clinical History.—A white male infant, weighing 4015 gm., was born on July 21, 1928. The mother had been well during pregnancy, a para II, the first born, a male, four years of age, was living and well. The mother's Wassermann reaction was negative, and there was no history of miscarriages, or stillbirths.

At birth it was noted that the cry was feeble, respirations rapid, and the skin cold, and pale, with a slight yellow tinge. Jaundice developed a few hours after birth, and increased rapidly until death, 72 hours later. The infant was feeble at birth, and toxicity increased with the jaundice. The extremities were limp and atonic, and reflexes were depressed, no signs of increased cerebral tension were present, and there were no convulsions. Spleen and liver were palpable and the splenic enlargement became quite marked. The infant refused the breast, and was fed with difficulty from a medicine dropper. Meconium stools were passed, and the urine was a dark yellow brown color. The temperature was normal throughout. Twenty cc. of whole blood were injected intramuscularly into the glutei, with no favorable response on the part of the infant, who became moribund and expired 72 hours after birth.

The blood findings were as follows: Hemoglobin (Sahli) 56 per cent, red blood cells, 2,510,000, of which there were between 90,000 to 115,000 nucleated red blood cells per cubic millimeter. There was marked variation in the size, and slight change in the shape of the erythrocytes, and diffuse basophilia, and the immature cells varied from very early proerythroblasts to normoblasts. Occasional punctate basophilia was noted (Fig. 3).

The white blood cells numbered 25,600, and the differential count showed 58 per cent polymorphonuclear neutrophils, 1 per cent eosinophils, 36 per cent lymphocytes, and 5 per cent large mononuclear cells. Platelet count was, 75,000 per cu. mm. Coagulation time was prolonged to 10 minutes, 30 seconds, and

bleeding time extended over 2½ hours. *Fragility test*—hemolysis starts at 0.42 per cent. *Urine* gave a 2 plus bilro test, otherwise normal

Postmortem Examination—(Dr Paul Cannon, at Chicago Lying In Hospital.)

Gross Anatomy—Well developed full term male infant weighing 4015 gm. Marked generalized icterus gravis over the skin of entire body are bluish mottlings. There is marked edema of the subcutaneous tissues. The scrotum is engorged with fluid. There are no external marks of trauma, except needle puncture marks in the buttocks. Umbilical cord appears normal. Subcutaneous tissues contain more than normal amount of fat.

Abdominal Cavity—It contains about 15 c.c. unclotted blood together with blood clots in the dependent portions.

Pleural Cavity—Free from fluid but parietal pleura contains diffuse areas of ecchymosis. The muscles are extremely pale.

Larynx and Trachea—The trachea is stained greenish.

Esophagus—The esophagus is normal.

Thyroid and Thymus—The thymus shows diffuse ecchymotic hemorrhages.

Heart, Aorta and Vessels—Foramen ovale is anatomically patent. The right atrioventricular cusps are normal. Heart weighs 30 grams. All orifices and cusps appear normal. The myocardium is extremely pale and is stained yellow.

Lungs—The visceral pleura contains numerous ecchymotic hemorrhages together with occasional larger areas of hemorrhage. The epicardium also contains diffuse ecchymoses. The lungs are not collapsed but air containing. They show no areas of consolidation or atelectasis. Cut surfaces are stained yellowish green and contain ecchymotic hemorrhages from 1 to 5 cm. in diameter. Lungs float in water. The bronchial mucosa contain fine petechial hemorrhages. Left lung weighs 29 grams, the right 42 grams.

Liver—It is enlarged and on the superior surface of lower lobe is a circumscribed area of white fibrous thickening extending about 1 mm. into liver substance. Liver tissue is greenish brown and is practically free from blood and weighs 240 grams. The gall bladder contains about 2 c.c. of bile which is extremely greenish and viscous. The bile ducts are patent and no obstruction to biliary or hepatic ducts could be found.

Spleen—The spleen is greatly enlarged and weighs 42 grams, is purplish and firm. Cut surface is cyanotic and firm, and shows no gross abnormalities. Cut surface also is rather dry.

Pancreas—Appears grossly normal.

Gastrointestinal Tract—Stomach, duodenum appear normal. The renal veins are anterior to aorta. The retroperitoneal tissue contains localized areas of hemorrhage.

Adrenals—The adrenals are greenish, but appear otherwise normal. They weigh 7.5 grams. The left preter is dilated to diameter of 6 mm. The right is normal in size.

Kidneys—The left kidney is extremely green particularly the cortical tissue being discolored. Otherwise appears normal. Right kidney resembles the left and together weigh 45 grams. The right tunical vaginalis testis contains about 5 c.c. of clotted blood. The left tunica vaginalis contains 2 c.c. of a greenish colored fluid.

Brain and Meninges—Skull and cranial tissues stain greenish and contain numerous petechial hemorrhages, particularly prominent in the temporal muscles. On opening the skull there is marked edema of leptomeninges which are stained greenish. Both hemispheres are pale. The leptomeningeal vessels are much paler than normal. There is no subdural hemorrhage. Falx cerebri is greenish and contains no hemorrhages. The tentorium cerebelli are intact. There is increased amount of

greenish stained fluid just beneath tentorium. The brain is extremely edematous. The lateral ventricles contain normal quantity of greenish fluid. The brain tissue proper is extremely soft and greenish yellow.

Histologic Examination Liver—Shows a great many areas of large cells with deeply staining nuclei, which are embryonic blood forming cells, forming hematopoietic foci (Fig 1). These hematopoietic areas are thickly scattered throughout the liver tissue in the tracts and various parts of the liver lobules. There is considerable destruction of liver cells, most marked in the periphery of the liver lobules. The liver cells contain considerable light brown staining pigment (bile pigment), and considerable deposits of greenish pigment (iron) are scattered throughout in the reticuloendothelial cells. Many of the bile capillaries contain bile thrombi, both in the areas where there is liver cell damage, and also in those areas where the liver cells are uninjured.

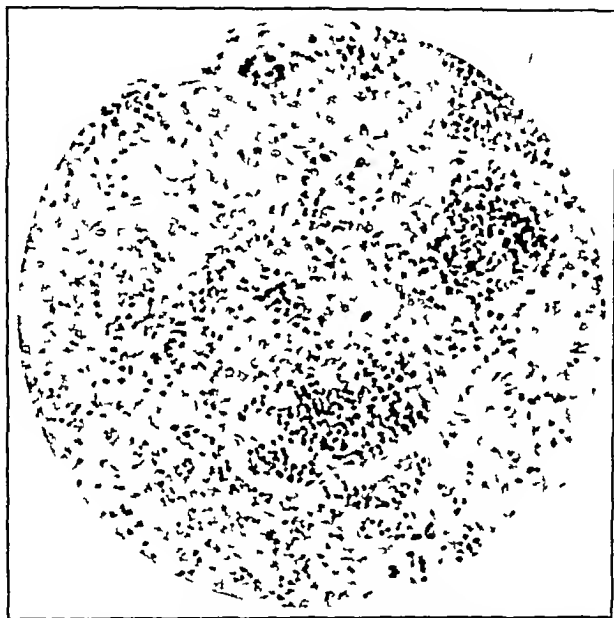


Fig 1—Microscopic section of liver from Case I of icterus gravis neonatorum. Clusters of cells with deep staining nuclei are embryonic hematopoietic foci. Deep staining liver cells contain bile pigment. (X250)

The diffuse hemopoiesis, the liver cells filled with bile pigment, the iron deposits, and the bile thrombi are the essential features in the histologic picture of the liver.

Spleen—Enormously engorged with blood. Many of the red cells are in phagocytes. The red cells appear abnormally granular. There are many eosinophils scattered diffusely. Young blood cells of all types are evidence of increase of blood forming tissue. Malpighian bodies are small but show no definite changes. Germinal centers not conspicuous. Many of the macrophages contain pigment. There are a few cells resembling marrow cells.

Bone Marrow—Shows normal areas of hemopoiesis of the red and white elements.

Lung—Alveoli contain much protein precipitate but there is no evidence of inflammation. Most of the alveoli are expanded.

Thymus.—Contains large numbers of eosinophiles especially in the stroma. There is some interstitial hemorrhage and edema. No other recognizable changes.

Adacy.—Tubular epithelium swollen and granular with much protein precipitate. There are many casts in the straight tubules granular and heavily pigmented. Mostly reddish brown. No inflammatory changes.

Pancreas.—Occasional eosinophile scattered throughout the stroma and in the islets. No other recognizable changes.

Adrenal.—The cells in the central part of the cortex are much vacuolated and seem to be somewhat disintegrated. There are a few small areas showing extravasation of blood. No inflammatory changes.

Cerebellum.—No changes, except that some small vessels contain hyaline thrombi.

CASE 11—Clinical History.—(From the Infant Ward, Sarah Morris Children's Hospital, Service of Dr. J. Gerstler). A white female premature infant weighing 2130 gm. of eight months gestation was born on April 20, 1933, the seventh child. Pregnancy was uneventful, labor was precipitate and rapid. Both the mother's and father's Wassermann and Kahn reactions were negative. There were six previous pregnancies in this family. The first child, born twenty-one years ago, was a full term infant because jaundiced on the second day and died on the third day of life; the second child was born nineteen years ago, an eight months premature stillbirth, not jaundiced and no edema noted; the third child was born seventeen years ago, a jaundice noted, died of pneumonia on the twelfth day of life; the fourth child was born fifteen years ago, a full term infant, jaundiced on the second day and died on the fourth day of life; the fifth child was born twelve years ago, a full term normal male infant, living and well; the sixth child was born eleven years ago, a full term male infant, jaundiced, was noted almost immediately after birth. Red blood cell count 1,100,000, white blood cell count 9,800, PMN 41 per cent, lymphocytes 27 per cent, eosinophiles 1 per cent, and myelocytes 1 per cent. The infant was given several transfusions of mother's whole blood intraspinally and recovered. The child is now living and well and normal in all respects. There was no history of hydrops universalis in any of the 6 children in this family.

The premature infant here reported was transferred to the premature station where a progressively deepening jaundice developed. The liver was palpable two finger breadths below the costal margin and the edge of the spleen was firm. The infant was fed with difficulty, meconium stools were passed and the urine stained the diapers darkly but none could be obtained for examination. Ten cc. of whole blood were injected intramuscularly on April 20 and ten cc. were given on April 22. The infant bled profusely from the nose and expired 48 hours after birth.

The blood findings were as follows. At 8 hours of age hemoglobin (Newcomer) was 41 per cent, red blood cells 2,600,000 of which there were 113,000 nucleated red blood cells per cubic millimeter. There was marked polkiloctosis and slight anisocytosis, there was diffuse basophilia and many reticulated red blood cells were demonstrated with vital staining. There were numerous very early nucleated red blood cells. The white blood cells numbered 92,500 and the differential count showed 54 per cent polymorphonuclear neutrophils, 1 per cent eosinophiles, 1 per cent basophiles, 7 per cent myelocytes, 2 per cent myeloblasts, 31 per cent lymphocytes and 1 per cent large mononuclear cells. Coagulation time was over 10 minutes and bleeding time extended over one hour. *Fragility test*.—hemolysis started at 0.50 per cent and was complete at 0.34 per cent.

Icterus index was 123 units and both the indirect and direct Van den Bergh reactions were immediately positive. At death 48 hours after birth the red blood count had dropped to 790,000 and the hemoglobin to 22 per cent (Newcomer).

Blood Iron—Blood iron determined by the Fowweather method was 40.5 mg per 100 cc at 8 hours of age and 15.9 mg per 100 cc at 48 hours. Calculated hemoglobin from blood iron was greatly higher than hemoglobin determined by the Newcomber method.

BLOOD IRON AND CALCULATED AND DETERMINED HEMOGLOBIN

	BLOOD IRON MG/100 C C	HGB (NEWCOMBER) GM/100 C C	HGB (CALCULATED) GM/100 C C	HGB RATIO FE
8 hours	40.5	8	13.5	1.16
48 hours	15.9	3.5	5.3	1.38

(Calculated hemoglobin in grams per 100 cc is obtained by multiplying blood iron by factor 335.)

POSTMORTEM EXAMINATION

(Dr Marion Corrigan, at Michael Reese Hospital)

Gross Anatomy—The body is that of a fairly well developed, premature (seven months' gestation) female infant weighing 2000 grams and measuring 48 cm. Liver and rigor mortis are absent. The skin and sclera are deeply icteric. There are several punctate hemorrhagic spots on the skin of the forehead.

On section, the skin is elastic, the subcutaneous fat tissue negligible.

The pleural, pericardial, and peritoneal cavities show no gross changes.

The heart is of normal size. The valvular apparatus is intact. The myocardium is firm brownish red. The foramen ovale and ductus arteriosus are patent. The intima of the entire aorta is colored deep yellow.

The lungs are semi-firm. The pleural surfaces are smooth. The surfaces of the lungs are mottled and dark red. Only small portions of the lung margins are pink gray. The sectioned surfaces are dark red, smooth but for occasional small raised granular areas. The trachea and bronchi show no changes.

The liver is firm, brownish red, and the surfaces smooth. On section, the surfaces are brownish red, the markings poorly defined. The gallbladder and bile ducts show no changes. The liver weighs 110 gm.

The spleen is markedly enlarged and weighs 50 grams. It is purple red, and on section the trabeculae are easily discernible, the follicles obscure.

The kidneys are purple gray, firm, and lobulated. On section, the medulla is well defined from the cortex. In the medulla are glistening plaques of yellow tissue. The pelves, ureters, and bladder show no changes.

The uterus, tubes, and ovaries show no changes.

The pancreas, adrenals, and thymus show no changes.

In the mucosa of the ileum are a few hemorrhagic areas, otherwise the gastrointestinal tract shows no changes.

On opening the calvarium, the meninges are seen to be somewhat hyperemic. In the basal nuclei are shining yellow streaks and plaques, *Kern icterus*. There is no evidence of hemorrhage.

The marrow of the long bones appears deeply red.

HISTOLOGIC EXAMINATION

Heart—Sections of the myocardium stained with hematoxylin-eosin show no histopathological changes other than the presence in the blood vessels of many immature cells.

Lungs—There is some extravasation of red blood cells into the subpleural spaces. Most of the alveoli are filled with red blood cells and dark brown granules. These

granules are largely free in the alveolar spaces a few being mononuclear cells. The bronchi contain many red blood cells and masses of pink staining material (fibrin) in the meshes of which are mononuclear cells. At the margins of the hemorrhagic areas the alveoli are dilated and confluent.

Liver.—The sections stained with hematoxylin-eosin show the cytoplasm of the parenchymal cells vacuolated and containing numerous dark brown pigment granules. The sinusoids are dilated, the Küpfer cells filled with brown granules. In the bile capillaries are many bile thrombi. Scattered through the sections are accumulations of cells located in the sinusoids. In sections stained by the Giemsa method these cells show the characteristics of myelocytes nucleated red blood cells undifferentiated mononuclear cells, and occasional large polynuclear cells (megakaryocytes).

Spleen.—In the sections of spleen the differentiation between follicles and pulp is obscured, the lymphoid tissue diffuse. Throughout the sections are seen many immature cells and a large amount of brown pigment some of it within mononuclear cells, some extracellular.

Kidneys.—In the tubules close to the glomeruli the lining cells are swollen and most obliterating the lumen. Occasionally the cytoplasm of these cells contains dark brown granules. Stained by Mallory's ferrocyanide method, these granules appear Prussian blue (iron).

Suprarenals.—There is some extravasation of blood into the medulla.

Pancreas and Thymus.—No histopathologic changes.

Bones.—(Femur) The epiphyseal lines are fairly straight. The medullary spaces are filled with mature and immature cells and occasional osteoid giant cells. Many cells are seen very close to the periosteum.

Brain.—The sections through the basal nuclei reveal some increase in vascularity. There are dark brown pigment granules within the ganglion cells.

REVIEW OF CLINICAL SIGNS AND SYMPTOMS

The most striking clinical manifestation of icterus gravis neonatorum is *jaundice*. It may be faintly present at birth but rapidly increases in severity and intensity during the first hours after birth.¹⁴ It is unusual for the icterus to develop later than the first twenty-four hours after birth which is a differentiating feature from physiologic icterus neonatorum which generally appears after the third day of life.

The rapidly developing icterus stains the skin, sclerae and mucous membranes to a deep yellow brown color which reaches great intensity within twenty-four to forty-eight hours after birth. This extremely rapidly developing and pronounced jaundice is the most striking sign of the disease.

Many of the reported cases of icterus gravis neonatorum have been well-developed, full term infants as the case of the infant here described though a considerable number have been prematurely born. Symptoms of the disease are often present at birth the cry may be feeble the infants are often drowsy and toxic difficult to arouse refuse or are unable to take the breast or bottle. In contrast to those with *somnolence*, flaccidity and hypotonicity some occasionally develop clonic contractures opisthotonos and generalized convulsions as signs of cerebral irritation. These latter manifestations are par-

ticularly associated with those infants who develop the nuclear or "Kern icterus"^{10 1 18} No one who has ever seen such a newborn infant, afflicted with this intense jaundice, will deny that the infant is desperately ill

Occasionally a slight *edema* may be noted in these jaundiced infants which is of quite a mild degree, and involves the extremities, chiefly the hands and feet *Petechiae* and more extensive ecchymoses have also been noted on the skin as well as hemorrhage from the mucous membranes of the mouth and nose Bleeding has also been reported from the umbilical stump and intestinal tract, and is probably associated with the prolonged bleeding time frequently noted

Cases of icterus gravis neonatorum have been reported, as of either *familial* or *sporadic* type, in fact its occurrence in successive pregnancies has led to the inclusion of the "familial" or the "habitual" type of icterus gravis neonatorum as a descriptive title of the disease Nevertheless, sporadic cases are of recognized occurrence

The disease is known to occur in many *races* and cases have been reported from infants of English Dutch German, Scandinavian, Russian, and Italian parentage The first cases reported in the American literature were in 1916¹⁰ Recently an authentic case of Chinese parentage has been reported²¹ DeLange⁹ reports a family in Groningen in which a mother lost two children with icterus gravis neonatorum in preceding pregnancies, and was finally delivered of twins The first a boy, developed icterus gravis neonatorum and the second, a girl, was born with hydrops congenitus universalis

Hilgenberg²² reports a *mother* who had several normal children by her first marriage, and gave birth to six infants who died of icterus gravis neonatorum by her second marriage On the other hand, E V Gierke²³ reports the case of a *father* who had a normal daughter by his first marriage, and by his second wife two newborn infants who succumbed shortly after birth and were found at autopsy to have suffered with icterus gravis neonatorum There is good evidence then to point to the *familial* nature of the disease, though *sporadic* occurrences have also been noted The two families quoted in which second marriages occurred might point to a hereditary factor In Hilgenberg's report the mother had normal children by her first marriage, and the *second husband* would be implicated On the contrary, in V Gierke's report the father had a normal daughter by his first wife, so that the *wife of the second marriage* would be suspected of the hereditary transmission Though the familial tendency can be definitely stated, there are too few reports to assume a hereditary transmission

Besides the signs and symptoms already mentioned, enlargement of the liver and spleen is usually noted, the latter being enlarged considerably, and of a firm consistency

Hematologic findings are of great interest. The anemia is of a severe degree and the pallor is quickly masked by the deep jaundice. It is of a hyperchromic type, the color index being 1 or above. There is a rather marked poikilocytosis with only slight anisocytosis. The white blood count is moderately increased with little change in the differential count and occasional immature white cells are found.

The most important and characteristic change in the blood picture is the enormous number of immature and nucleated red blood cells found in the circulating blood, from 50,000 to over 100,000 per cu mm. They vary from the very early erythroblasts to normoblasts and basophilic red cells and the nuclei of these immature erythrocytes show many mitotic figures. A few of these early erythrocytes are probably proerythroblasts.²¹ A possible relationship between the presence of these many immature erythrocytes in the blood with the extramedullary erythropoieses will be discussed later. A greatly increased number of reticulocytes may be demonstrated in smears stained with vital stains.

The platelets are diminished in number averaging 80,000. Combined with this relative thrombopenia we note a slightly increased clotting time and a greatly increased bleeding time, which probably accounts for the tendency to skin ecchymoses, hemorrhage from the mucous membranes and the petechiae found on the internal serous surfaces and in the viscera. The first blood iron determinations to be reported in a case of icterus gravis neonatorum, are those from Case II here presented. The blood iron values obtained were considerably higher than would be expected for the determined grams of hemoglobin per 100 cc (Newcomber).

The resistance of the red blood cells to various saline concentrations is little changed. The icterus index of the blood serum is greatly increased and a biphasic Van den Bergh reaction is usually present. The Wassermann and Kahn blood reactions in these cases are both negative. We may summarize the characteristic blood findings as severe hyperchromic anemia of hemolytic origin, marked erythroblastic blood picture as evidenced by the immature red blood cells, increased number of reticulocytes, thrombopenia and greatly increased bleeding time and an increased amount of bile pigment and iron in the circulating blood.

The urine has in the majority of cases shown a positive test for bile pigment indicating the obstructive as well as the hemolytic origin of the jaundice.

The placenta has been reported as enlarged in a number of the reports^{2, 4, 10, 21} with a yellowish vernix caseosa covering the infant at birth.

A fatal outcome has ensued in the majority of reported cases though the eventual termination may depend upon the severity and

ticularly associated with those infants who develop the nuclear or "Kern icterus"^{16 17 18} No one who has ever seen such a newborn infant, afflicted with this intense jaundice will deny that the infant is desperately ill

Occasionally a slight *edema* may be noted in these jaundiced infants which is of quite a mild degree, and involves the extremities, chiefly the hands and feet *Petechiae* and more extensive ecchymoses have also been noted on the skin, as well as hemorrhage from the mucous membranes of the mouth and nose Bleeding has also been reported from the umbilical stump and intestinal tract, and is probably associated with the prolonged bleeding time frequently noted

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Besides the signs and symptoms already mentioned, enlargement of the liver and spleen is usually noted, the latter being enlarged considerably, and of a firm consistency

The liver cells, themselves, have been found to be deeply stained with bile pigment. There are areas of liver cell damage, marked by cell necrosis and some fatty degeneration of the liver cells. The Kupffer cells contain considerable amounts of iron pigment.

Bile thrombi crowd the bile capillaries, and have been reported in numerous cases (see Fig 2). Iron deposition in the reticuloendothelial cells is pronounced and is associated with the phagocytosis and lysis of the erythrocytes in these cells.

Spleen and kidneys show marked accumulations of iron pigment, as well as some extramedullary hematopoietic areas, as do the pancreas, thymus, adrenals and some other organs.^{2, 3, 4, 5, 11}

The bone marrow may show normal to increased^{1, 12} degrees of white and red blood cell hematopoiesis and some diminution in the megakaryocytes.^{4, 5, 11}

THEORETIC DISCUSSION OF PATHOLOGIC FINDINGS

It would be interesting to speculate on the relationship of the various pathologic findings and I offer the following theoretic possibilities:

1 *Icterus*—As has been previously noted, Mann¹² and his coworkers have shown that hemoglobin is broken down in the reticuloendothelial cells and in the blood stream, to form bilirubin which is then taken out of the blood by the epithelial liver cells and is stored and excreted by them into the bile capillaries and thence into the larger hepatic ducts. The epithelial liver cells, therefore, do not form or *secrete* bilirubin; they simply store and *excrete* this pigment.

Similar in many ways to kidney excretion, the liver cells must excrete the bilirubin brought to them by the blood stream and jaundice will not occur if excretory demands are sufficiently met in the *absence of obstruction of the bile passages*. It might be possible that jaundice in the absence of obstruction can then be caused by bilirubin being produced faster than normal liver cells are able to excrete it. Further, it might be caused by *disturbed or damaged* liver cell excretory ability with a normal rate of formation of bilirubin which cannot be removed satisfactorily. It can be further pointed out that there may be an actual diminution in the number of liver cells through destruction or necrosis without a *resulting* jaundice if the remaining hepatic cells are able to excrete bilirubin normally. However, while a damaged liver may be capable of ridding the blood of a *normal* amount of bilirubin, such a liver would be unable to excrete an *excess* production of this pigment and jaundice would result from the retention of this material.

I have previously pointed out that normally, with the onset of labor, a gradual and continuous destruction of the polycythemic fetal blood occurs, and blood destruction goes on in the newborn at an increased

rate. This must result in an increased bilirubin formation during the first few days of life, and is probably one of the chief causes of physiologic icterus neonatorum. A damage to the epithelial cells of the liver in icterus gravis has been described since the early report of Pfannenstiel²⁵ and has been confirmed by nearly all subsequent reports. The increase in bilirubin formation together with the damaged liver cells, may produce icterus in the absence of obstruction to bile ducts.²⁶ This may be demonstrated by an indirect Van den Bergh reaction: presence of increased urobilin and absence of bilirubin and bile salts in the urine. This would not explain the bile pigment in the urine, and the positive direct Van den Bergh reaction.

The presence of *bile thrombi* in the bile capillaries (Fig. 2) will aid in this explanation. The direct Van den Bergh reaction and the presence of bile pigment in the urine can only be accounted for on the basis of an obstruction to the flow of bile in the bile passages. Bloom²⁸ has shown that following complete obstruction of the common bile duct experimentally, the increasing amount of bilirubin in the blood gives at first, only the indirect and later the biphasic Van den Bergh reaction. The obstructed bile fills the small bile ducts and diffuses into the lymph spaces and then into the blood stream. An actual rupture of the bile capillaries need not take place. The plugging of these bile capillaries by bile thrombi may be sufficient to cause a reflux of bilirubin into the lymph spaces and blood stream.

As an explanation for the jaundice, we may, therefore, conclude that an increased bilirubin production, and an impaired excretion result in a *retention* icterus; the bile thrombi explain the *obstructive* or *regurgitation* icterus, and all signs and tests indicate a combination of these two mechanisms in the production of jaundice in icterus gravis neonatorum.

I have accounted, in part, for the increase in bilirubin excretion, as a physiologic phenomenon, occurring normally at birth. What causes the liver cell damage and what the bile thrombi?

It is apparent from a microscopic examination of the liver that we are dealing with an organ abnormal for a full-term or premature infant. The tremendous number of hematopoietic foci simulate the embryonic organ of a fetus of from three to five months' gestation.^{5, 20} I can only believe, from a study of the cases in the literature and those here reported, that we are dealing with a fetal type of liver, which for unknown reasons, has failed to mature properly. There is no evidence to suggest that the liver has developed normally, and that the hematopoietic foci are of a compensatory nature. The bone marrow shows no changes indicating incapacity. Further, any such compensatory process developing shortly before and after birth would hardly be conceivable in so short a time.

Another explanation offered suggests that the overcrowding of the liver with hematopoietic foci could cause pressure atrophy and damage to the liver cells enough to cause obstruction as well as hemolytic jaundice.¹¹ If this were possible, would not every embryonic liver be overcrowded? would not obstructive jaundice occur in every leukemic infiltration in Niemann Pick's disease in every metastatic liver carcinomatosis and in diffuse hemangio endotheliomata?

An arrested fetal development of the¹² liver may be due to a defective anlage and possibly the familial occurrence of this condition may be sought for in germ plasim defect. Toxic influence early in pregnancy¹³ as in congenital syphilis might also retard liver growth and cause the arrested fetal development.¹⁴

It may be supposed that in this condition the embryonic liver takes care of bilirubin excretion until near the end of pregnancy be it of premature or full term duration. The fetal hematopoietic foci in the liver augment the blood cell formation from the bone marrow and immature red blood cells are thrown into the circulation.¹⁵ Increased bilirubin formation added to decreased ability of epithelial liver cell excretion must lead to an intruterine bile retention. Thus we may term Stage I. Accumulation of excess bilirubin in the bile capillaries perhaps mixed with a foreign protein substance,¹⁶ leads to coagulation of bile pigment in the bile capillaries and thus to bile thrombi. Occlusion of the bile capillaries by bile thrombi leads to a diffusion of bilirubin into the lymph spaces and into the blood stream and thus we have bile regurgitation. Stage II. Though the fetal kidneys secrete but little urine, there is proof that the amniotic fluid contains some fetal urine.¹⁷ The bile regurgitated into the blood stream is eliminated by the fetal kidney into the amniotic fluid. This explains the beer brown amniotic fluid and the golden yellow vernix caseosa. The increased number of fetal erythrocytes reduces the oxygen-carrying power of the blood and by increasing anoxemia may cause the enlargement of the placenta noted in this disease and in congenital hydrops neonatorum.^{18 19 21}

Should the process only proceed as far as Stage I due to the ability of the liver epithelial cells to excrete sufficiently to keep up with bilirubin formation an infant will be born with only a variable degree of hemolytic or retention icterus which may not be present at birth and which will probably be a mild form of icterus gravis neonatorum with a favorable chance for recovery. This also answers Klemperer's²¹ query as to the differences in liver pathology which may occur in this disease. Returning to the question what causes the liver cell

The most common pathologic change in the liver of congenital syphilis is its general retardation of development. The liver in newborn congenital syphilis is still actively engaged in blood formation. MacCallum²² states "There is nothing clearly specific about such an anatomic picture—the same thing may be found in a normal fetus of a rather early stage of development, but the abundant distribution of spirochetes through the tissue terminals its syphilitic nature."

¹True also in congenital syphilis.

damage? There may be impairment of the excretory power of the liver cells in anemia, and also in anoxemia²⁶ The increased number of circulating immature erythrocytes may augment fetal anoxemia, due to the less efficient oxygen-carrying power of young forms of red blood cells

The resulting anoxemic increase could produce liver cell damage, as MacCallum^{12b} and others have pointed out that damage to liver cells, especially in the area about the central efferent vein of the lobule, may be due to an insufficient supply of oxygen

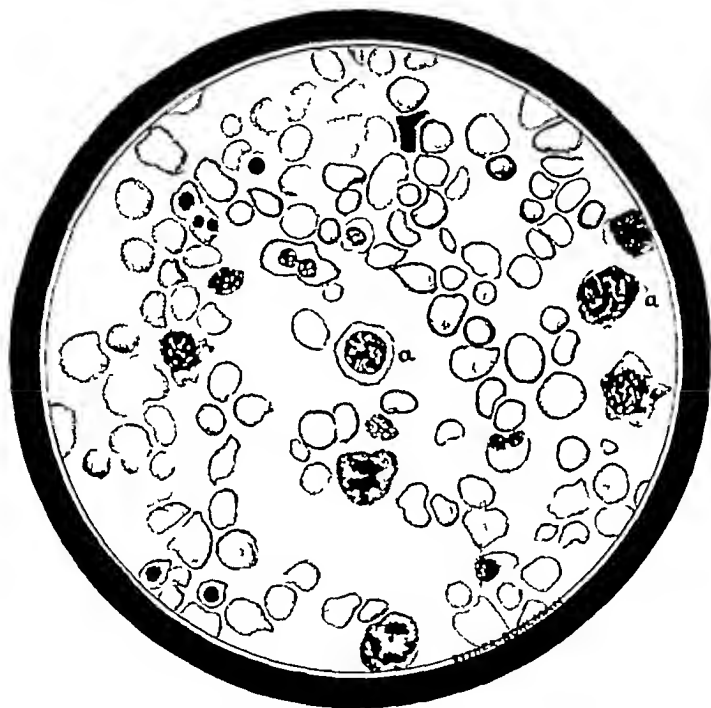


Fig 3—Blood smear from Case I of icterus gravis neonatorum at twelve hours of age. 90 000 nucleated red blood cells per cubic millimeter megaloblasts and normoblasts several of the latter undergoing cellular division. (a) are early erythroblasts Max Grunewald Giemsa stain

In some of the cases reported, the liver cell necrosis has been central, and anemia and anoxemia may account for this cell damage⁴ (Klemperer³¹—case 2) Bile stasis could probably also contribute to liver cell damage and necrosis Beginning with the arrested fetal development of the liver (possibly due to a defective anlage or toxic influence in early fetal development), I have thus far been able to offer a theoretical explanation for the jaundice the immature erythrocytes in the circulation, the degrees of jaundice with which the infant may be born, the variable antenatal severity of the disease, the familial incidence, the coloring of the amniotic fluid and vernix

caseosa the enlargement of the placenta, the bile thrombi, the liver cell damage, and the occurrence of a retention, as well as a regurgitation type of jaundice

We may explain the occurrence of *sporadic cases* on the assumption of toxic influence in early pregnancy rather than defective anlage

2 *The Iron Pigmentation*—This finding in the various organs may be due to the increased hemolysis of the red blood cells both in the circulation and in the reticuloendothelial cells, and may also be due to an increased phagocytic action on the part of this system. The increased destruction of red blood cells in the polycythemic fetal blood with the excess liberation, and destruction of hemoglobin, accounts for the increased iron in the circulation (Case II) and in the tissues. The breakdown of the excess hemoglobin liberates iron and this is picked up from the circulation by cells in the liver, spleen, kidney, tubules, pancreas, thyroid and other organs. The tissues of the body are simply oversupplied with iron, because of the excessive hemolysis of red blood cells and the resulting breakdown of hemoglobin throughout the circulation.

This whole process is in its essential points merely an accentuation of the hemoglobin destruction and iron storage, which normally occurs in the newborn period. Gladstone²² has recently reviewed this subject, and pointed out that Bunge's storehouse theory no longer holds, and that the newborn infant is not born with a fetal iron depot. It creates its own iron deposits after birth through the excess hemoglobin liberation and destruction when the change from the newborn polycythemia to the normal postnatal values for hemoglobin and red blood cells are taking place. Oxygen tension regulates this normal decline from the antenatal anoxicemic fetal polycythemia to the postnatal values commensurate with the environmental oxygen tension of air.

3 *Erythrocyte Resistance*—The relative fragility or resistance of immature erythrocytes also deserves discussion. DeLange⁴ has suggested that the youthful red cells have a greater resistance to hemolysis than mature erythrocytes. It has been mentioned that in icterus gravis neonatorum the fragility tests of red blood cells against various concentrations of saline solution varied little from normal. However, on closer analysis more facts are known than this, so that simply testing the red blood cells to saline dilutions and drawing conclusions from such tests is not enough. DeLange's suggestion of an increased resistance of youthful red blood cells is also held by Anselmino and Hoffmann²⁴ who propose the theory that the increased resistance of the youthful forms is offset by the decreased resistance of the older red blood cells. However, recent investigations tend to prove that exactly the opposite phenomenon is true, namely that the youthful red cells have a diminished osmotic resistance as compared to mature

erythrocytes.³ Thus decreased resistance might aid in explaining the rapid disappearance of the youthful forms.³⁶ Also any increased resistance would then be due to the older red blood cells. The whole subject of the normal osmotic resistance of the various aged erythrocytes as well as the changes in resistance which may occur in jaundice and other pathologic conditions needs much experimental proof, before conclusions can be adopted with certainty.

4 *Anemia*.—Discussion of the cause for the anemia in icterus gravis neonatorum may be brief, as the underlying factors have been already

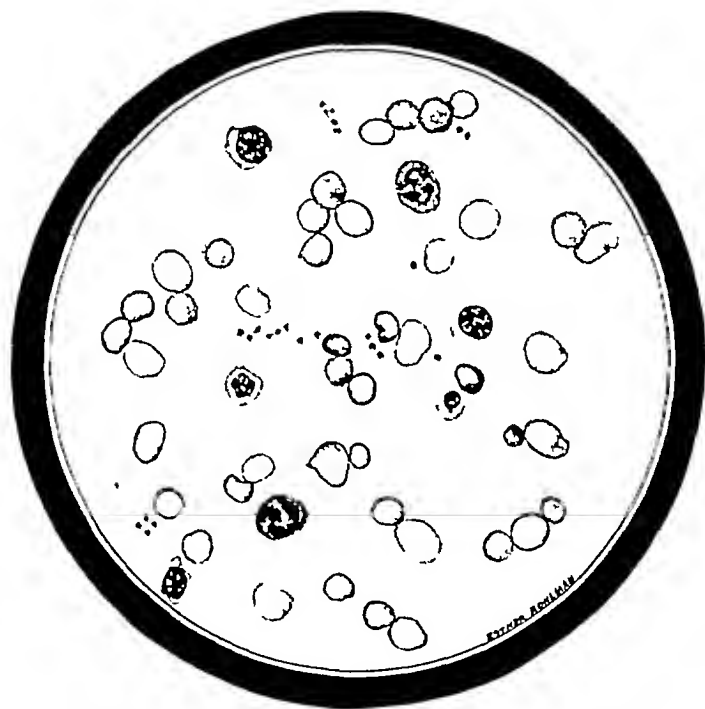


Fig. 4.—Blood smear from a case of anemia of the newborn at nine days of age. Hemoglobin 24 per cent, red blood cells 1,270,000, nucleated red blood cells 7800 per cubic millimeter. Max Grunewald, Giemsa stain.

traced in detail in the explanation of the occurrence of other signs and symptoms. It is assumed in this condition, that a normal polycythemia exists in the fetus, associated with circulating immature red cells.

The anemia is of a hyperchromic type, and the normal appearing hyperplastic bone marrow precludes an aplastic type of anemia. The normal fetal anoxemia is probably increased by the poorer oxygen-carrying capacity of the immature erythrocytes. The red blood cells in the reduced oxygen tension of high altitudes show, besides the polycythemia, some poikilocytosis, and hyperchromic characteristics. In

this type of polycythemia the color index is high, as it is also in the normal newborn. Even at heights over 7500 meters, nucleated red blood cells have not been found after careful and particular search.²⁷ The erythrocytes at high altitudes show outstanding regenerative, but no degenerative changes. The anemia of *icterus gravis neonatorum* is also of a hyperchromic type with no degenerative signs. The enormous increase in nucleated red cells is therefore not associated with lack of oxygen, polycythemia, bone marrow failure or developmental failure. The fetal extramedullary foci produce fetal types of nucleated red cells which may flood the circulation. When hemolysis begins with the

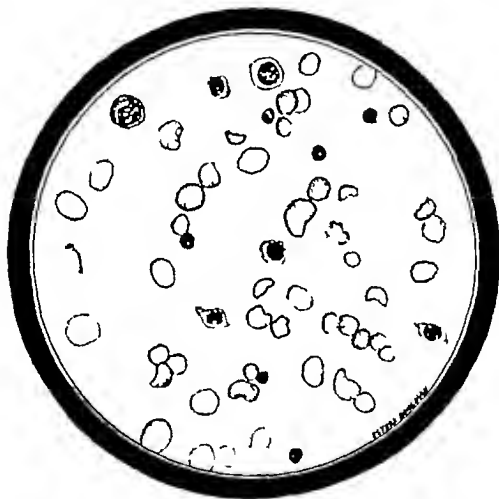


Fig. 5.—Blood smear from a case of congenital syphilis in a newborn infant 3 weeks of age. Hemoglobin 30 per cent, red blood cell 2,30,000, nucleated red blood cells 60,000 per cubic millimeter. Many normoblasts and extranuclear nuclei. Wright stain.

onset of labor, as in normal newborns, there is a rapid destruction of mature and youthful red cells. If we assume that the immature forms are more fragile, they must be destroyed at a more rapid rate in the increased oxygen tension after the onset of labor. The process is much too rapid for compensatory regeneration to be of immediate influence, though in infants who survive compensatory regeneration will aid after some weeks of life. The increasing jaundice probably adds to red cell fragility and increases the rate of hemolysis of the red cells. Extremely rapid red cell destruction for the reasons stated

accounts for the anemia. The circulating nucleated red blood cells are present in great numbers, for the same reason that they are similarly increased in other diseases where an embryonal persistence of hematopoiesis occurs, associated with enormous numbers of extramedullary blood islands (Fig 5). The cause of the arrested hematopoietic development is different in icterus gravis neonatorum, than it is in congenital syphilis, yet the source of the great numbers of nucleated red cells is probably the same in both cases. There is no necessity then, for assuming a primary metabolic disturbance of the entire hematopoietic system, or a compensatory origin of the extramedullary blood islands.³⁸ Hematopoietic foci are specific for, and outstandingly characteristic of, fetal liver. We have therefore, gone one step farther in the explanation of this condition, and if the facts be correct, the theoretic considerations must commence with the cause for the persistence of the embryonal type of blood formation.

ASSOCIATION OF ICTERUS GRAVIS NEONATORUM WITH OTHER ENTITIES

A Nuclear Icterus—The occurrence of nuclear or kern icterus associated with icterus gravis neonatorum¹⁶ probably depends upon the degree of jaundice. The condition never occurs in an adult, and is not exclusively linked with icterus gravis, as it has been noted in the brains of children dying after physiologic icterus neonatorum.^{17, 18} It has been thought that Kern icterus is responsible for the symptoms referable to the central nervous system, which occur in some of the infants surviving icterus gravis neonatorum. In Case II, here reported, a Kern icterus was found.

B Hydrops Congenitus Universalis—The similarity of hydrops congenitus universalis to icterus gravis has been pointed out in a number of reports.^{2, 11} In the former condition a diopsical infant is still-born, dies during birth, or may be delivered dead by cesarean section. The edema is universal and marked, there is pallor, and icterus may be slight, as noted in the edematous tissues. The blood from heart puncture shows greatly increased numbers of circulating immature erythrocytes. Pathologically the examination of the organs is similar to the changes found in icterus gravis. There are many petechial hemorrhages and ecchymoses. Extensive extramedullary hematopoiesis and hemosiderosis have been noted microscopically.

The liver shows the same number of hematopoietic foci as the liver of icterus gravis, and necrosis of liver cells and bile thrombi occur as frequently. It is interesting to note the occurrence of bile thrombi in combined reports of the two conditions. In reporting four cases of icterus (3 own and 1 literature), DeLange and Arntzenius⁴ noted bile thrombi in 4 cases out of 4. In reporting 6 cases of hydrops universalis where mention was positively or negatively made as to the occurrence of bile thrombi (1 own case and 5 literature), the same

authors reported their presence in 3 out of the 6 Salmonsens⁶ noted bile thrombi in 2 out of 5 of his reported cases of hydrops congenitus Ferguson⁷ noted bile stasis and thrombi in the bile capillaries in 2 out of 3 cases of icterus gravis, and none in two cases of hydrops congenitus Diamond Blackfan and Baty¹¹ report the autopsy protocols of 4 cases of icterus neonatorum gravis of which 1 (Case 9) was reported as having many bile capillaries distended with bile Slight edema has been noted in cases of icterus gravis neonatorum^{8 10 9 11} In Case I here reported edema of the subcutaneous tissues was noted and the scrotum was engorged with fluid The edema may be accounted for by such factors as severe anemia anoxemia or by an abnormal albumin globulin ratio, which have been used to explain edema associated with other anemias.¹¹ Since Plaut² reported siblings with icterus gravis and hydrops congenitus, other instances of the two diseases in the same family have been noted^{3 11} DeLange⁹ has reported twins one with icterus gravis and one with hydrops congenitus Common to both conditions are, the familial history, finding of each disease in a sibling the occurrence of edema in icterus gravis and of jaundice in hydrops congenitus, the similar pathology to the minute microscopic details, as hematopoietic foci hemosiderosis and bile stasis and thrombi in the bile capillaries and the focal liver cell necrosis and finally, the circulating immature red blood cells The two conditions must be assumed to be of identical etiology, associated with the persistence of an embryonal liver and blood formation. The more marked edema in hydrops oongenitus universalis is probably responsible for the intra uterine death in the majority of these cases

C Anemia of the Newborn—In 1931 Stransky¹² in reviewing the then published cases of this condition, noted the similarity in the pathologic findings reported by Frank¹³ and Schleussing¹⁰ to those of icterus gravis and hydrops congenitus He concluded that there were two types of cases one characterized by an embryonal blood picture and the other designated as an aregenerative type This analogy has since been made by several other authors^{11 11 14} In going over the literature I reviewed¹² the autopsy reports of Susstrunk¹² and Schleussing¹⁰ The former noted marked hemosiderosis and the latter numerous hematopoietic foci in various organs Since my report other cases of anemia of the newborn have appeared,^{11 14-20} of which the cases of Paschoff¹⁴ and Happ¹⁰ terminated fatally The postmortem findings in their cases also showed evidence of a fetal type of hematopoiesis

A familial tendency for the occurrence of anemia of the newborn in siblings has been noted by Diamond Blackfan and Baty¹¹ (Cases 6, 7 and 8), Segar and Stoeffler¹⁴ in 3 siblings Happ¹⁰ and Boner¹⁴ in 2 siblings each

A further relationship has been noted, in which different offspring of the same mother have suffered either icterus gravis or anemia. In Ecklin's¹ case of anemia of the newborn, the child of the preceding pregnancy had died of icterus gravis and Case 5 reported by Diamond, Blackfan and Baty¹¹ revealed that the first-born infant died of intense jaundice within 24 hours of birth.

It has been noted that many of the cases of anemia of the newborn have shown icterus. The second infant reported by Segar and Stoefler¹⁶ showed an edema of the scrotum on the fifth day, while in Case 8 of Diamond, Blackfan and Baty¹¹ edema of the eyelids and extremities was noted on the third day. We have then, in cases reported as anemia of the newborn a familial, as well as a sporadic type, besides the occurrence of icterus gravis or newborn anemia in offspring of the same mother, and finally the occurrence of edema in cases of anemia of the newborn. The anemia which is of varying severity is at first of a mild hyperchromic type with nucleated red blood cells moderately increased (see Fig. 4). Later the anemia tends to become slightly hypochromic. An infant surviving icterus gravis will gradually lose the hyperchromic type of blood picture, the immature erythroblasts will disappear from the circulating blood and a slightly hypochromic anemia will precede the return of the blood to normal. Van Creveld² has been able to demonstrate these changes by measuring the diameters of the red blood cells in three cases of icterus gravis and in one case of newborn anemia.

I would consider the occurrence of erythrophagocytosis in the peripheral blood as an incidental finding^{3, 11} and as pointed out this phenomenon has occurred in other unrelated diseases.³

D Association With Sepsis—Since the review by Knapfelmacher¹³ in 1910 sepsis of the newborn has been proposed as the etiologic basis for icterus gravis. Since then I. A. Abt,¹⁶ Yllpo,²⁰ Kleinschmidt and others have offered clinical proof and negative bacteriologic findings as evidence that icterus gravis is not based on sepsis. G. Meyer¹⁴ has recently reported two cases of newborn infants with deep jaundice who were shown to have died of generalized sepsis at autopsy. Dunham¹⁵ in a recent report on septicemia in the newborn, reported 12 infants in her series with severe jaundice and 3 instances of liver damage at autopsy (chronic hepatitis, diffuse fibrosis and central necrosis).

It cannot be denied that sepsis may cause jaundice and liver changes in the newborn, and that the clinical and pathologic findings may have some similarity with icterus gravis. However there have been enough cases of icterus gravis reported, where not even the minutest evidence of infection or sepsis could be found to warrant the negation of such an etiology. Newborn sepsis should be considered in the differential

diagnosis and with congenital syphilis should be excluded before the diagnosis of icterus gravis neonatorum is made

F. Prophylaxis and Therapy—Smyth⁴ has reported a most interesting attempt at prophylaxis in icterus gravis neonatorum. An Australian mother had previously given birth to nine infants the first two children were normal and survived there was one stillborn premature birth and 6 infants had developed icterus gravis neonatorum and died from 3 to 11 days after birth. A prophylactic attempt to prevent icterus gravis for the infant of the tenth pregnancy consisted of hospitalization of the mother through the entire course of her pregnancy with extremely careful supervision and regulation of her diet. The mother was perfectly normal during her term of pregnancy. Seven days before labor was due a cesarean section was performed and a normal female infant was delivered. The mother's tubes were resected and tied. The infant remained normal for twenty four hours when it became drowsy and progressively icteric and died 70 hours after birth.

This report is most instructive. It demonstrates the remarkable familial occurrence of the condition and the fact that the most careful supervision of the mother gives no clue to the disease of the fetus. The cesarean section precludes all possibility of a vaginal infection of the infant and is strong evidence against the septic origin of the disease. Further the resection and tying of the tubes in a woman who has had eight newborn infants die out of 10 pregnancies would seem a wise eugenic procedure.

Bernheim Karrer and Groh²³ have reported the daily feeding of 100 grams of liver to a mother during the last 10 weeks of her pregnancy who had previously given birth to two newborn infants dying of icterus gravis. A normal infant was born following the liver feeding prophylaxis but no conclusion can be drawn from such an isolated instance as in Smyth's⁴ case the mother was also fed liver during her pregnancy and the infant born died of icterus gravis.

The question of blood transfusion as a therapeutic measure in icterus gravis is open to analysis. Infants to whom blood had been given therapeutically have both survived and succumbed. Kramsztyk²⁰ has reported recovery of a case after intramuscular injection of 10 cc of whole blood. Others have given transfusion and intramuscular blood to these infants with and without success.^{7 10 11 21 27} (Cases here reported.) Spontaneous recovery has also been reported in cases of anemia of the newborn as well as survival after transfusion.¹²

Splenectomy has been attempted by Cooley²⁸ in a case of icterus gravis. While the removal of the spleen might slow blood destruction in this condition it could hardly be expected to prove of much aid in a severe case.¹⁶

SUMMARY

In the course of the discussion the similarity in symptoms, signs and pathologic findings, though meager, pointing to the relationship of icterus gravis neonatorum with hydrops congenitus universalis and anemia of the newborn have been brought out. A theoretic explanation has been offered to account for the known clinical and pathologic findings in icterus gravis neonatorum. In the absence of definite substantiating facts, a speculative etiology, *embryonal persistence of hematopoiesis of erythrocytes* has been advanced, which would explain the findings in icterus gravis and the interrelationship of the three conditions on the same causative basis. Beginning with the persistence of an embryonal characteristic in the fetus, the resulting disease may be explained on the degree of the process in each individual case. An analogy with congenital syphilis, a disease of known etiology, could here be drawn. (a) An extensive early spirochetal action may result in a macerated fetus or stillbirth. Early embryonal fetal persistence of hematopoiesis of erythrocytes may result in hydrops congenitus universalis. (b) A newborn congenital syphilitic infant may be less severely damaged than the macerated fetus or stillborn, and it may show jaundice, and immature circulating erythrocytes (Fig 5). An embryonal persistence of a somewhat later stage than hydrops congenitus may result in icterus gravis neonatorum. (c) A congenital syphilitic infant may show an early severe anemia. A slight degree of embryonal persistence may result in anemia of the newborn.

CONCLUSION

The three clinical entities described as icterus gravis neonatorum, hydrops congenitus universalis and anemia of the newborn show interrelated clinical signs and symptoms, most significant of which are familial occurrence, jaundice, edema, anemia and circulating immature red blood cells (erythroblastosis).

The pathologic findings in these three diseases show a certain similarity, but the facts are too meager to permit drawing definite conclusions, and nothing is known of the essential prenatal pathology of the three diseases.

The classification and origin of these three newborn conditions has been vague and uncertain. A theory is offered, embryonal persistence of hematopoiesis of red blood cells in various organs, which would explain the clinical symptoms and pathology common to these three newborn entities.

The inferences drawn are purely speculative and must await future pathologic or experimental proof. The origin of the extramedullary hematopoietic foci in the various organs appears to be an embryologic persistence rather than a compensatory regeneration of erythrocytic

foci While the term erythroblastosis has been used by previous authors, I believe that embryonal hematopoietic persistence would be more accurate and better descriptive of the underlying disturbance

Two cases of icterus gravis neonatorum associated with circulating immature red blood cells in a marked degree are here added to similar cases already reported The first case was of sporadic occurrence, and revealed no nuclear involvement in the brain, the second was of the familial type and associated with Kern icterus

Blood iron determinations not previously reported for icterus gravis neonatorum were found to be high in the second case here presented

REFERENCES

- 1 Czerny, Ad and Keller A Handbuch des Kindes Ernährung ed. 2 Leipzig and Vienna 1923, F Deuticke vol. 1 p 194
2. Von Gierke, E. V. (a) Verhandl. d. deutsch path. Gesellsch 18 322 1921
(b) Klin. Wchnschr 50 2295, 1931
3. Plant A. Arch Path 4 13, 1927
- 4 DeLange C. and Arntzenius, A. Jahrb f Kinderh. 124 1, 1929
- 5 Kleinschmidt, H. Klin. Wchnschr 9 1951, 1930
6. Salomonsen L. Ztschr f Kinderh 15 181, 1931
- 7 Sanford H N. Am. J Dis. Child. 41 225, 1931
- 8 Ferguson, J A. Am J Path 7 277 1931
- 9 DeLange C. Acta Pediat. 13 292 1932.
- 10 Clifford, S H. and Hertig, A.: N. E. J. Med. 207 105 1932
- 11 Diamond, L. K. Blackfan, K. D., and Baty J M. J Pediat. 1 200 1932.
12. Strankey E. Ztschr f Kinderh. 51 239 1931
- 13 Knoefelmacher W. Ergebn. d. inn. Med. u. Kinderh. 5 205 1910
- 14 Meyer, Gustav. Arch. f. Kinderh 98 143 1933
- 15 Dunham E C. Am J Dis. Child. 45 229 1933
16. Abt Isaac A. Am J Dis. Child 13 231 1917
- 17 Orth J: Virchows Arch. f. path. Anat 63 447 1875
- 18 Glaser, Jerome. Am. J Dis. Child 36 10, 1928
- 19 Mann et al. Am. J Physiol. 69 393 1924 Ibid. 78 384 1926.
- 20 Ylipä A. Ztschr f Kinderh. 17 334, 1918
21. Ku, D Y and Li Y. Virchows Arch. f. path. Anat. 283 62 1932
- 22 Hillgenberg F. Monatschr f Geburtsh u. Gynäk. 70 261 1925
- 23 Von Gierke E. V.: Virchows Arch. f. path. Anat 275 330 1930
- 24 Maximow A. A., and Bloom William. Textbook of Histology Philadelphia 1930 W B Saunders & Co p 116 Fig 86 (cell 22)
- 25 Aschoff L. Klin. Wchnschr 39 1670 1932.
26. Rich, A. R. Bull. Johns Hopkins Hosp 47 340 1930
- 27 Pfannenstiel, J. München med. Wchnschr 55 2169 and 2233 1908
- 28 Bloom William. Bull. Johns Hopkins Hosp 34 316 1903
- 29 MacClure E. Ztschr f Kinderh 51 80, 1931
- 30 Williams, J Whitridge. Obstetrics, ed. 4 Appleton, 1920 pp 168-168 DeLee J B. Principles and Practice of Obstetrics ed 3 1920, W B. Saunders Co., pp 68, 69
- 31 Klemperer P. Am. J Dis. Child. 628 212 1924
- 32 MacCallum W R. Textbook of Pathology ed. 2, 1920 W B. Saunders Co., (a) 742 (b) 490-492
- 33 Gladstone, S. A. Am. J Dis. Child. 44 81, 1932.
- 34 Anselmino and Hoffman. Arch Gynäk 143 47 1931 Ibid. München. med. Wchnschr 79 1226, 1932
- 35 Goldbloom A., and Gottlieb. Am. J Dis. Child 38 57 1920
- 36 Brock, J. Biologische Daten für den Kinder Arzt, Berlin, 1932, J Springer, pp 94, 95
- 37 Hartman Hans. Klin. Wchnschr 12 453 1933.
- 38 Brannan Dorsey. Bull Johns Hopkins Hosp 41 104 1921
- 39 Frank, E S.: Nederl. Tijdschr v Geneesk. 70 1384 1926
- 40 Schleussing H. Verhandl. d. deutsche path Gesellsch 21 371 1926

- 41 Finkelstein, Heinrich *Jahresk f Artzl Fortbild* 23 1, 1932
- 42 Abt, Arthur F *Am J Dis Child* 43 347, 1932
- 43 Susstrunk, G *Ztschr f Kinderh* 38 587, 1924
- 44 Paschoff, H D *Am J Dis Child* 42 111, 1931
- 45 Pritchard, E, and Smith, J *Arch Dis Child* 6 325, 1931
- 46 Dalldorf, G, and Russel, H K *N Y State J Med* 32 839, 1932
- 47 Akerrren, Y *Acta Pediat* 14 142, 1932
- 48 Segar, Louis H, and Stoeffler *J Pediat* 1 485, 1932
- 49 Bonar, E B, and Smith, E H *Am J Dis Child* 45 594, 1933
- 50 Happ, Wm H *J Pediat* 1 648, 1932
- 51 Ecklin, T *Monatschr f Kinderh* 15 425, 1919
- 52 Van Creveld, S *Am J Dis Child* 44 701, 1932
- 53 Abt, Arthur F *Am J Dis Child* 42 1364, 1931
- 54 Smyth, J S *M J Australia* 2 268, 1931
- 55 Berheim Karrer, J, and Groh M *Ztschr f Kinderh* 50 672, 1931
- 56 Kramsztyh, H *Ztschr f Kinderh* 51 273, 1931
- 57 Rosenbaum, Harold *Arch Pediat* 45 621, 1928
- 58 Cooley, T B *J Pediat* 1 640, 1932

104 SOUTH MICHIGAN AVENUE

THE DISAPPEARING TIME OF DYES INJECTED INTRADERMALLY

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SOME of the theories of vital staining have been considered by Krebs and Wittgenstein^{12, 20} and von Möllendorff.¹¹ For our purposes we have to keep in mind that the chemical constitution of a dye as such does not seem to have much to do with its distribution; that acid and basic dyes on the whole behave differently and that the size of the particles of a dye in its solution is of importance. Schultze¹ offered the suggestion that the distribution of various substances in the organism including acid dyes might be dependent on their common property of carrying a negative electric charge and their being attracted therefore to anodal regions of the organism.

That the electric charge of the particles of dye is of the greatest importance to their behavior has been accepted by others as for instance Krebs and Wittgenstein,^{12, 2} Werthamer and Fischer.² The electrical factor has been stressed particularly by Keller. He proposed to discontinue the division of dyes into acid and basic dyes and to distinguish them according to their migration in the electric field, as cathodal or anodal dyes. Most of the acid dyes wander to the anode in watery solution; the basic dyes to the cathode. But in blood serum or in cell plasma the direction of the migration can change so that acid dyes become cathodal and basic dyes anodal. By means of dyes it is possible to determine whether a cell or tissue is preponderantly positively or negatively charged. The importance of such a distinction is readily seen. For instance according to Keller a very important factor in the transportation of water in the organism is its migration to the cathode.

Such considerations prompted our experiments to determine whether it was possible to differentiate in this sense an easily visible part of the body for example the superficial layer of the skin. It was thought that intradermally injected dyes depending on their character might be retained for a shorter or longer period of time (Table I).

The dyes were injected into the skin of the forearm of volunteer subjects, using 0.2 cc. in a 0.01-100 solution made up in 0.5-100 so

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dium chloride solution. Occasionally stronger solutions were used. Each dye was tested on at least three persons. Keller tested a large number of dyes on the smelling rods, and then joints, of *Daphnia magna*, listing those which stained the rods cathodal and those which stained the joints anodal. Of the errors he mentions, we encountered particularly irritation on injection of some of the dyes (Table I).

The group of cathodal dyes contains only acid dyes, and the group of anodal dyes contains basic dyes with the exception of aurantia (Table I).

The disappearance is often gradual and cannot be determined with great accuracy. The limits of time can be regarded only as approximate, nevertheless, they were sufficiently distinct for our purpose. With Congo red, for instance, this difficulty depended to a certain extent on the color of the skin of the subject. Proper color filters could be employed with advantage. With brilliant kresyl blue some color remained for weeks in the needle stab and in a few experiments with isamine blue, for days.

The first consideration must be given the degree of dispersion of the dyes, since a coarsely divided dye is more likely to remain at the place of injection. The relative size of the particles has been determined by various methods, such as ultrafiltration,³ elevation in strips of filter paper, penetration into gelatin,¹⁰ and their rate of diffusion.⁴ The degree of dispersion depends also on various factors such as temperature, concentration, reaction, and presence of salts or of colloids.

TABLE I

TIME OF RETENTION OF VARIOUS DYES IN THE SUPERFICIAL LAYER OF THE SKIN

CATHODAL DYES	TIME OF RETENTION	ANODAL DYES	TIME OF RETENTION
Fluorescein	2 to 4 hr	Malachite green	1 to 2 hr
Eosin	12 hr	Neutral red	12 hr
Erythrosin	48 hr	Aurantia	Less than 24 hr
Rose bengal	36 to 60 hr	Aniline green	More than 6 hr
Rubin S	Less than 24 hr	Methylene blue*	36 to 72 hr
Litmus	Less than 24 hr	Neutral acriflavine	3 to 5 days
Azolitmin	Less than 24 hr	Fuchsin basic	5 days
Congo red	48 to 96 hr	Dahlia	6 days
Trypan red	48 to 96 hr	Safranine	2 weeks
Fuchsin acid	5 days	Brilliant kresyl blue	Weeks
Alkali green	2 months		
Water blue	2 months		
Alkali blue	More than 1 yr		

*The methylene blue kept its blue color for this length of time whether any leukobase was formed cannot be said.

At present it seems hardly possible to determine the size of the particles very accurately under various conditions, and so it is easily understood that authors differ in the arrangement of the dyes in the order of the size of the particles.

Fluorescein is generally said to be finely divided whereas alkali blue is one of the coarsely divided dyes. Fluorescein disappeared rather rapidly, whereas alkali blue remained for a very long time. But Congo red, rather coarsely divided, disappeared sooner than the more finely divided fuchsin, whereas neutral nonflavine and basic fuchsin disappeared more slowly than the more coarsely divided neutral red. Such observations indicate that the degree of dispersion is not likely to be always the determining factor of the disappearing time.

Some dyes, like rubin S, gave a weak color in the dilution used. Bismarck brown and neutral violet gave color that was too weak for reading. In some instances higher concentrations were used, fluorescein, in a concentration of 1:1000 disappeared in seven hours, and aurantia, in a dilution of 1:5000, disappeared in less than twenty-four hours. Neutral violet, in a concentration of 1:1000 caused irritation as did a number of other dyes. Occasionally, Congo red proved a little irritating in a dilution of 1:10,000. With this dye rather numerous tests were made. Injections of alkali green were followed by some edema. Litmus and azolithmin were irritating, although a purified litmus was used. In stronger concentrations, both were very irritating, producing local edema and reddening. Elman, Drury and McMaster prepared erythrolein and erythrolitmin from litmus. We used erythrolein in a dilution of 1:2000, but it could hardly be seen and it produced no irritation. Erythrolitmin in dilution of 1:10,000 disappeared in thirty to sixty hours. In this dilution it was not irritating. Stronger solutions, 1:5000 and 1:1000 were painful and irritating. The disappearing time was prolonged, indeed, the injection of 1:1000 could still be seen after months.

Litmus, azolithmin and erythrolitmin turned blue on injection and remained so. But this can hardly indicate the actual reaction of the superficial skin, since Elman, Drury and McMaster showed that erythrolitmin has a great salt and protein error.

Safranin, not irritating on injection, produced in all instances slight superficial necrosis with scaling. Neutral acriflavine behaved similarly. In concentrations of 1:1000 it produced infiltration.

Fühner remarked that many dyes are irritating and can produce inflammation. Of our dyes aniline green produced by far the most intense reactions, being also very painful on injection. In a few experiments with rabbits the effects of its instillation into the conjunctival sac, and of its intracutaneous injection, was compared with malachite green and iodgreen, also basic dyes. In a dilution of 1:10,000 these latter dyes did not produce inflammatory reactions, while aniline green did. In stronger concentrations, aniline green produced hemorrhagic inflammation in joints and the pleural cavity.

It may be mentioned that iodgreen, injected into one subject, disappeared within twelve hours

Comparing the disappearing time of fluorescein, rose bengal, eosin, erythrosin, and fuchsin S, all cathodal dyes, with that of neutral red, basic fuchsin, methylene blue and perhaps acriflavine and safranin, all anodal dyes, it appeared hardly possible to distinguish the superficial layers of the skin in the sense which Kellei meant. The more coarsely divided dyes were left out of consideration. Neither acid nor basic fuchsin was discolored. The colorless carbinol of fuchsin was not restored to color. According to Karczag, this would indicate indifference with regard to electric charge.

Furthermore, in his more recent work, Bennhold stated that the migration of acid and basic dyes in serum goes in the same direction in the electric field. Under these conditions it is rather questionable whether the direction of migration in the electric field is concerned preponderantly with the disappearance time of dyes on intradermal injection of normal persons. It is still possible that among the various factors which determine the disappearing time of dyes, electric influences play a part.

Hudack and McMaster stated that intradermal injections are predominantly intralymphatic. Lymphatic capillaries in regions injured in various ways are far more permeable than usual. Serum added to the vehicle retards the penetration of dye from the lymphatic structures to the interstitial spaces. We added Congo red and methylene blue to serum of man so that the concentration of the dye was approximately 0.01:100. This was done by adding 0.1 cc of 1:500 solution of dye to 2 cc of serum. Under these circumstances the dye spread more easily and disappeared more quickly. For instance, in forty-eight hours, Congo red mixed with serum had entirely disappeared when injected into three subjects, whereas when mixed with physiologic serum it was still visible in seventy-two to ninety-six hours. Methylene blue mixed with serum disappeared in twenty-four hours, while mixed with salt solution it could be seen from thirty-six to seventy-two hours. These results are in accord with other experiments. After intravenous injections of Congo red, the dye appears in the wheal produced by mechanical irritation of the skin or by intradermal injection of histamine or codeine,^{8, 17} and it disappeared more rapidly than we expected from the intensity of the color.

It is by no means certain that spreading in the lymphatic structures is the only factor concerned here. Bennhold has shown that different dyes dissolved in serum penetrate into gelatin to an equal distance in a given time, even if in watery solution they show great variations dependent largely on the size of the particles.

This difference may explain, at least partially, the slow disappearance time of Congo red in cases of edema in which the edema fluid

is poor in protein. In some children with nephrotic edema the color was distinctly visible after one to two weeks. The dye did not spread as much as usual. Congo red in serum seemed to disappear more rapidly, also, in cases of edema. In a case of lymphedema of the right leg the dye disappeared in three days from both legs. So far the number of our observations with dyes in various diseases is too small to permit consideration.

Such tests may become useful, since it has been shown by Höber and Banus, Mond, Wertheimer, Keller, and others, that change of conditions may change the permeation of dyes in cells and membranes.

CONCLUSIONS

The disappearance time of dyes injected into the superficial layers of the skin of normal persons does not seem dependent on their direction of migration in the electric field. Neither can a definite distinction be made between acid and basic dyes. Within certain limits the degree of dispersion does not seem the deciding factor.

Congo red and methylene blue dissolved in serum disappears more rapidly than when dissolved in salt solution.

REFERENCES

1. Bennhold, Hermann. *Ergebn. d. inn. Med. u. Kinderh.* 42: 273, 1932.
2. Elman, Robert, Drury O. R. and McMaster P. D. *J. Exper. Med.* 47: 777, 1928.
3. Fischer, F. P. *Arch. f. Augenh.* 100: 101, 480, 1929.
4. Fischer, F. P. *Arch. f. Augenh.* 103: 554, 1930.
5. Fühner, H. In: Heffter A. *Handbuch der experimentellen Pharmakologie*, Berlin, J. Springer, 1923, 1, 1199, 1296.
6. Gellhorn, Ernst. *Arch. f. d. ges. Physiol.* 221: 230, 10-8, 1929.
7. Höber, Rudolph and Banus M. G. *Arch. f. d. ges. Physiol.* 201: 14, 1923.
8. Hoff, Ferdinand. *Ztschr. f. d. ges. exper. Med.* 57: 253, 1927.
9. Hudack, S. S. and McMaster, P. D. *Proc. Soc. Exper. Biol. and Med.* 29: 944, 1932.
10. Kurezug, L. *Methoden der Elektrople*. In: Abderhalden, Emil. *Handbuch der biologischen Arbeitsmethoden*. Abt. 5 Teil 2 Part 1: 831, 974, 1928.
11. Keller, R. *Ergebn. d. Physiol.* 30: 204, 1930.
12. Krebs, H. A., and Wittgenstein, A. *Arch. f. d. ges. Physiol.* 212: 283, 1926.
13. Krebs, H. A., and Wittgenstein, Anneliso. *Ztschr. f. d. ges. exper. Med.* 49: 563, 1926.
14. Möllendorff, Wilhelm. *Ergebn. d. Physiol.* 18: 141, 1920.
15. v. Möllendorff, W. In: Abderhalden, Emil. *Handbuch der biologischen Arbeitsmethoden*. Abt. 5 Teil 2, Part 1: 97, 152, 1928.
16. Mond, Rudolf. *Arch. f. d. ges. Physiol.* 206: 172, 1924.
17. Pilcher, J. D. *Am. J. Dis. Child.* 31: 77, 1926.
18. Schulemann, Werner. *Biochem. Ztschr.* 80: 1, 1917.
19. Wertheimer, E. *Arch. f. d. ges. Physiol.* 200: 354, 1923.
20. Wittgenstein, Anneliso and Krebs, H. A. *Ztschr. f. d. ges. exp. Med.* 49: 553, 1926.

Ibid. *Ztschr. f. d. ges. exp. Med.* 49: 537, 1929.

BODY BUILD IN INFANTS WITH ACUTE INTESTINAL INTOXICATION

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BY BODY build is meant the external form of the body as determined by the skeletal parts. No attempt will be made here to critically evaluate previous studies on this subject. It will suffice to state (1) that hitherto studies have been largely qualitative and have depended for the most part on subjective interpretations, and (2) that modern statistical methods for expressing and evaluating data have not been generally applied. Attempts have been made to describe body build in terms of indices, i e, the proportion of one dimension to another, as the cephalic index $\left\{ \frac{\text{cephalic breadth} \times 100}{\text{cephalic length}} \right\}$, the facial index $\left\{ \frac{\text{facial breadth} \times 100}{\text{facial height}} \right\}$ etc, but the indices hitherto used have not yielded results of statistical reliability. The use of indices in children is complicated by the factor of growth which results in a continuous change in the relation of one dimension to another.

In the present study the simple expedient of relating the various dimensions to total body length has been adopted. The value of this device will be apparent when the data are presented below.

A difficulty in the study of body build is the choice of dimensions to be measured. Since qualitative studies of body build lay emphasis on "laterality" versus "linearity" in describing body configuration¹ dimensions were chosen which measure this quality, i e, the bimalar and bigonial diameters of the face, the biacromial and bicristal diameters of the trunk and the circumference of the chest at the nipples. These measurements are taken from bony points and hence errors due to nutritional status are minimal. A large number of other dimensions have also been measured but these have not yet been evaluated.

The technic for making the measurements has been described in full elsewhere.² The dimensions used in this paper were measured as follows:

1. Diameter of face (bimalar) The horizontal distance between the two malar prominences.

2. Bigonial diameter of face The horizontal distance between the most distant points of the angles of the jaw, perpendicular to the midsagittal plane.

3. Biacromial diameter Straight distance between the most lateral points of the acromial eminences, taken from behind with the child seated, the arms close to the thorax.

From the Children's Medical Service of Bellevue Hospital and the Department of Pediatrics, New York University and The Fifth Avenue Hospital.

4 Bicristal diameter Straight distance between the most lateral points of the iliac crests, perpendicular to the midsagittal plane

5 Circumference of the chest at nipples. Taken halfway between inspiration and expiration. The respiratory excorcion of the chest of a quiet infant is small

Measurements of the external dimensions of healthy infants were made in order to establish norms with which to compare sick infants. The group of well infants comprises abandoned infants, infants left in the hospital because of unsuitable home conditions, and infants admitted to the hospital with mild upper respiratory infections. There were 397 males and 347 females. The patients with acute intestinal intoxication, as well as the healthy infants, were from a poverty stricken group, and were measured shortly after admission to Bellevue Hospital.

In an earlier study¹ the various measurements for all well infants under 1 year were recorded in relation to total body length and aver

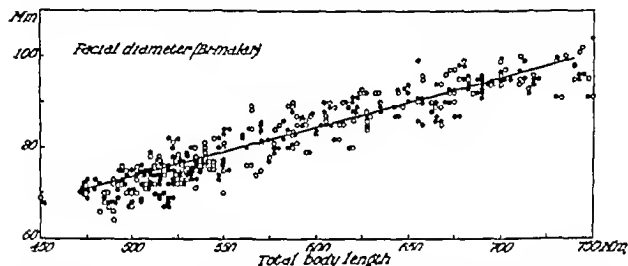


Chart 1.—The relation between total body length and the bimalar diameter of the face during the first year of life. Dots represent individual measurements on females, the circles on males. The continuous line is the curve of central tendency

ages and standard deviations calculated by various subdivisions of body length as illustrated in Chart 1 for the bimalar diameter of the face. A curve of growth for the body dimension in question, in relation to total body length, was then constructed by connecting the points representing the average values. Dimensions of the infants with acute intestinal intoxication were compared with these curves and the reliability of the differences tested statistically. These differences were found to be significant.

Since growth during the first year of life is rapid the reliability of grouping together all infants in this age period may be questioned. Growth curves for the various lateral dimensions have been constructed therefore, for smaller subdivisions of age under 1 year and it is with these groups that the sick infants are here compared.

Description of Clinical Material—Acute intestinal intoxication is here used to designate a type of reaction in infants characterized by

somnolence alternating with periods of hyperirritability, by acidotic hyperpnea and by evidence of dehydration. There is usually cyanosis and oliguria or anuria. Fever and an associated infection are frequently present and anorexia, vomiting and diarrhea are usual. Convulsions are occasionally observed. There are no characteristic gross anatomical changes, except, perhaps, in the liver.

The cases were collected over a period of 3 years, for the most part during the winter months. The distribution of cases by season of the year is shown in Table I.

TABLE I

	NUMBER OF CASES	PERCENTAGE OF DEATHS
January February	30	70
March April	41	73
May June	56	61
July August	19	47
September October	40	60
November December	34	53
All Months	220	62

There were 119 males and 101 females all of whom were under 1 year of age. Sixty-two per cent of the infants died. Only children of Caucasian parents are included in this study since the body build of colored infants is known to be different. Sixty-two patients (28 per cent) were measured before the onset of acute intestinal intoxication.

Most of the infants showed evidence of upper respiratory infection. In addition the following associated conditions, shown in Table II, were present:

TABLE II

ASSOCIATED CONDITION	NUMBER OF CASES	ASSOCIATED CONDITION	NUMBER OF CASES
Mastoiditis	1	Scurvy	1
Pneumonia	22	Tetany	1
Eczema	5	Peritonitis	1
Erysipelas	1	Pylorospasm	2
Pyuria	4	Prematurity	3
Emphysema	1	Total	42

In Chart 2 the height of infants with acute intestinal intoxication (dotted line) is compared with the height of the healthy infants (continuous line) from the same social environment. The averages for the sick infants are regularly below those for the healthy.

In Charts 3, 4, 5 and 6 the lateral dimensions of infants with acute intestinal intoxication, represented by dots, are compared with the healthy, in relation to body length, for various subdivisions of age under one year. Continuous lines represent the average values for

healthy infants. The dotted lines represent one standard deviation on each side of the average and include 68 per cent of the healthy infants. Data are shown only for the first 24 weeks of life. The number of cases after this age period was too small to be of significance.

Dimensions of the infants with acute intestinal intoxication tend to fall below the average lines for the healthy indicating that infants with acute intestinal intoxication are relatively smaller in their lateral dimensions than are the healthy infants. No difference was found for the horizontal diameter of the trunk in the present enlarged series or in the series previously reported.

Infants measured while well, who subsequently developed acute intestinal intoxication showed the same body configuration as the infants measured when ill and are included with the sick infants. The infants with acute intestinal intoxication who died showed no differences from those who survived.

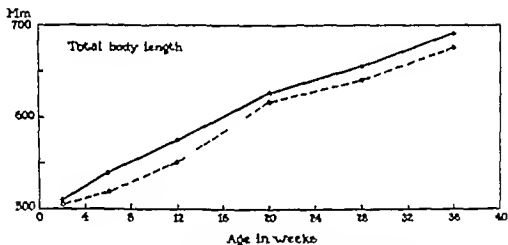


Chart 2.—Comparison of the total body length of healthy infants (continuous line) and infants with acute intestinal intoxication (dotted line).

The relative narrowness of infants with acute intestinal intoxication is not characteristic of all sick infants. As has been previously shown⁴ in infants with tetany and in infants with eczema the lateral dimensions are relatively larger than in the healthy infant.

A rational basis for the difference in the body build of infants with acute intestinal intoxication may be deduced from a comparison of the growth of two groups of healthy infants from different social environments. In addition to the healthy group already described, a series was studied in a "well baby" clinic at the Fifth Avenue Hospital. The infants were derived from families of moderate income and were observed from birth through the first year. The racial make up of the two healthy groups was similar and has been shown to be without influence on the dimensions measured.⁵

It was found that the infants in the well baby clinic group were superior both in weight and height to the healthy infants in the poverty group. It was also found that, for various subdivisions of age,

the poverty group infants were smaller in their lateral dimensions than were those from the well baby clinic

From these results it may be stated that, when in a group of infants, a delay in growth occurs, the delay is more marked for the lateral dimensions than for the cephalocaudal. These results, on the one hand, a change in body build, the delayed group becoming relatively smaller in their lateral dimensions, and, on the other hand, a

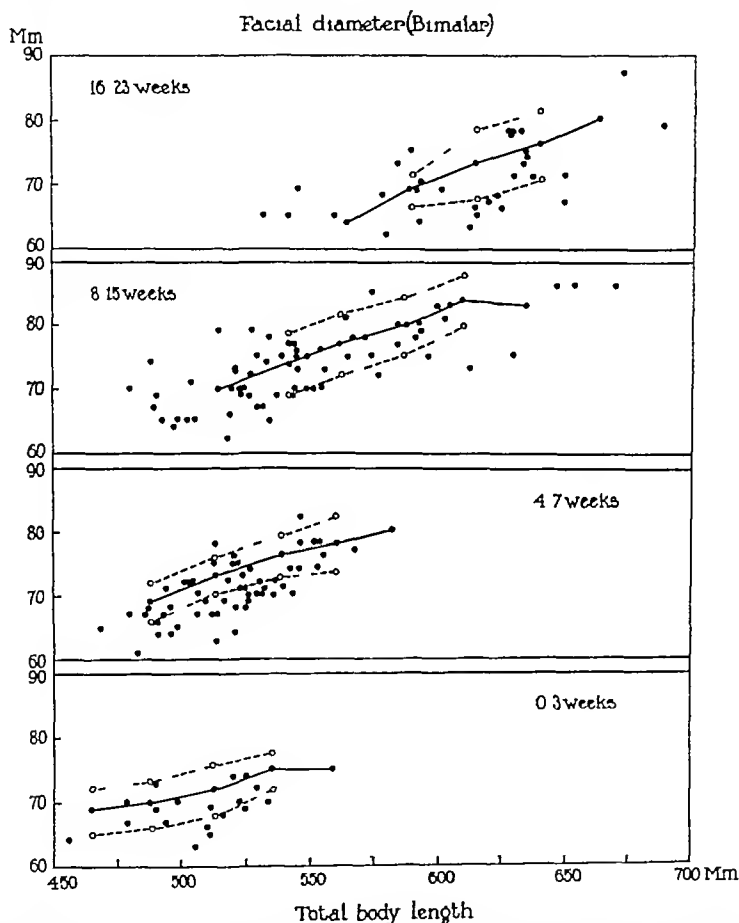


Chart 3—The relative width of the face (bimalar diameter) in infants with acute intestinal intoxication. Continuous lines connect the average values for healthy infants. Dotted lines represent one standard deviation on either side of the average. Dots represent infants with acute intestinal intoxication.

susceptibility to the development of acute intestinal intoxication. It has long been known to pediatricists that when a retardation of growth occurs in infants, all parts of the organism are not equally involved, the delay in growth of weight being more striking than the delay in growth of height. The infants with acute intestinal intoxication were compared with the Bellevue Hospital group, itself a delayed group

Had the comparison been made with the "well baby clinic" group the differences would have been much more marked

About 18 months ago a well baby clinic was established in the poverty district. Only infants born in Bellevue Hospital were treated. The incomes of the families were similar to those of children in the hospital group. The results of this study will shortly be published in detail. It may be here stated that the values for the well baby clinic at Bellevue Hospital were identical with those obtained in the well

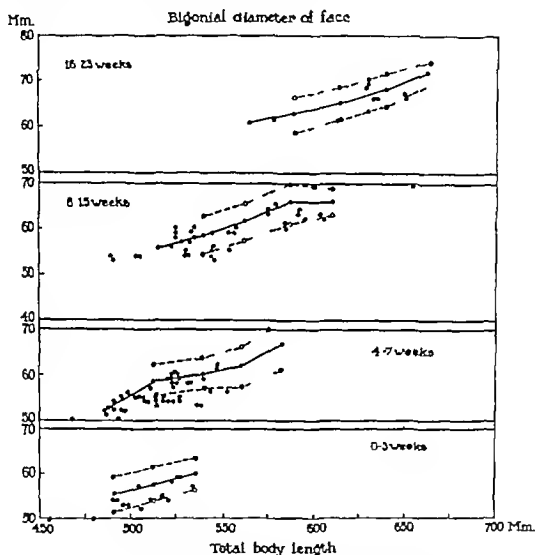


Chart 4—The relative diameter at the angle of the jaws (bilgonial diameter) in infants with acute intestinal intoxication.

baby clinic at the Fifth Avenue Hospital the Bellevue district group growing as well in height and weight and having the same body proportions as the Fifth Avenue Hospital group

The relation of deficient diet to the etiology of acute intestinal intoxication Acute intestinal intoxication tends to occur in infants who are shorter and relatively smaller in their lateral dimensions than are healthy infants. That this type of body build results, in part, from environmental influences is borne out by the two groups of studies mentioned above: (1) the differences in body build of two groups

of healthy infants of similar racial make-up but from different social environments, and (2) the change in body build in a group of healthy infants from a poverty-stricken environment following the institution of a health clinic. It seems reasonable to assume that the prominent environmental factor introduced by the health clinic was diet. Whether acute intestinal intoxication results from inadequacy in the

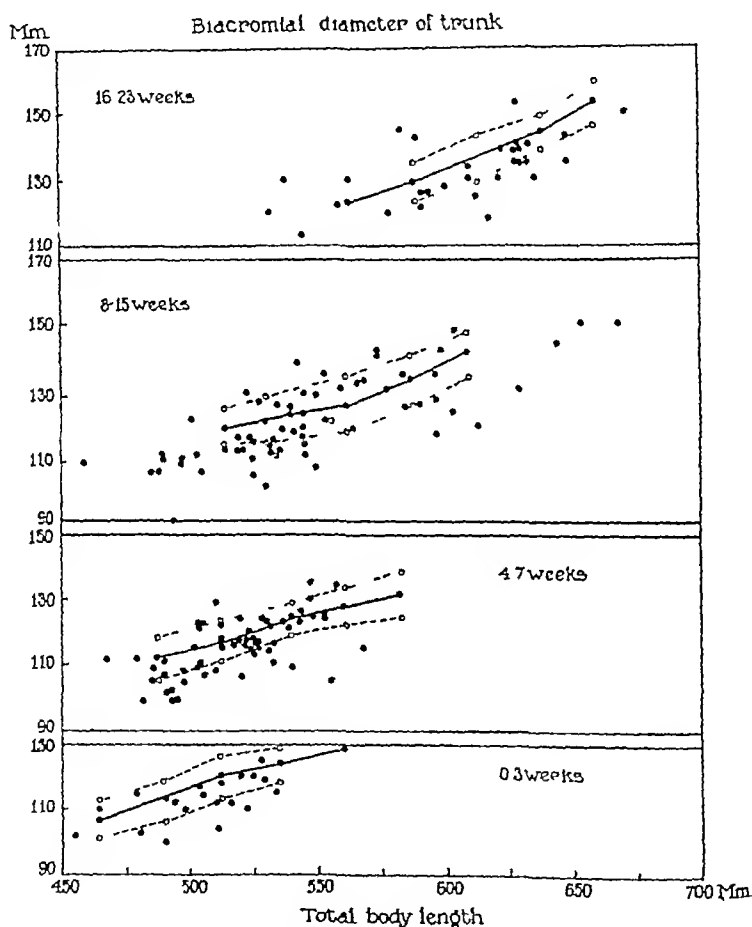


Chart 5—The relative width of the shoulders (biacromial diameter) in infants with acute intestinal intoxication

amount of energy-producing substances in the diet or from a deficiency in a specific food factor cannot be stated.

Infants with the growth changes herein described, when exposed to infection (as occurs frequently during the winter months) or to high external temperatures (during the summer months), react with the disease syndrome known as acute intestinal intoxication. In this respect there is a close analogy to tetany which is frequent until made manifest by an infection.

The mechanism by which a dietary inadequacy leads to acute intestinal intoxication is as obscure as the mechanism by which any of the known vitamin deficiencies lead to disease

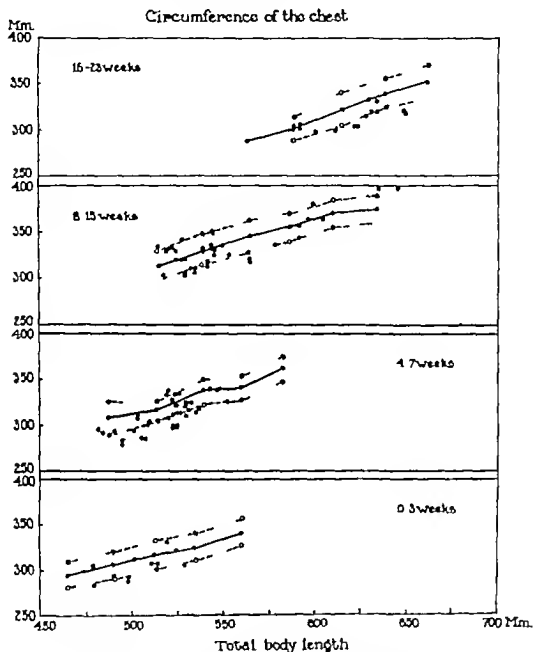


Chart 6—The relative circumference of the chest in infants with acute intestinal intoxication

SUMMARY

1 Infants with acute intestinal intoxication are, on the average shorter than healthy infants from the same social environment

2 In relation to total body length, infants with acute intestinal intoxication have narrower faces, narrower shoulders and smaller chests than healthy infants

3 The proportion of the dimensions mentioned above to total body length in infants with acute intestinal intoxication is determined, in part by a retardation of growth

4 Since deficient diet leads to retardation of growth, it is reasonable to look upon acute intestinal intoxication as causally related to dietary deficiency

REFERENCES

- 1 Stockard, C R Am. J Anat 31 261, 1923
- 2 Bakwin, H , and Bakwin, R M J Clin Invest 10 369, 1931
- 3 Bakwin, H , and Bakwin, R M J Clin. Invest 10 377, 1931
4. Bakwin, H., and Bakwin, R M. J Clin. Invest 10 395, 1931

132 EAST SEVENTY FIRST STREET

ACRODYNIA

A NOTE ON THE PATHOLOGIC PHYSIOLOGY

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THE clinical syndrome which is now called acrodynia, although first described in 1903,¹ escaped attention until recent years, when it was recognized independently in widely separated geographical locations and designated by a number of descriptive titles. Among the names which have been used to designate this bizarre condition, some at least should be mentioned:

Trophodermatoneurosis (Selter) 1903

Erythroedema (Swift) 1914

Swift's disease

Pink disease (Clubb)

Acrodynia (Weston) 1920

Polyneuritic syndrome resembling pellagra (Byfield) 1920

Vegetative neurosis (Feer) 1923

Feer's disease (Erickson)

Dermatopolyneuritis (Thursfield)

The first series of cases to receive prominence was that reported by Swift in 1914.² Not until 1920 were descriptions of the disorder published in the United States. Following the reports by Bilderback,³ Weston⁴ and Byfield,⁵ references to this apparently new disease appeared in the literature in rapid succession.*

In Europe the first descriptions appeared in the literature in 1921.⁶ Among the many contributions to this subject in the years of recognition and definition, the careful observations and added information concerning the disease contained in the studies of Feer in 1922⁷ and subsequently, mark these papers as of outstanding importance. However, the conception of the author of the pathogenesis did not immediately receive widespread acceptance.

As in any recently described disease, the typical severe example has become readily recognized, but only in the light of accumulated ob-

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References to acrodynia in the literature exceed 150 available articles of which 40 or more were published in this country. It is manifestly impossible in a short note to review the literature in any detail and to give adequate credit to authors for priority as regards descriptions of features of the clinical picture of the disease.

servation and experience are the variations in the clinical picture, and particularly the mild and borderline cases, clearly defined. It is the purpose in this paper to consider briefly certain features of acrodynia as observed in a series of forty-four cases seen in this clinic within the past nine years, and to correlate so far as permissible the clinical manifestations of the disease with the pathologic physiology.

Acrodynia is a disorder, encountered in infants and young children, of gradual onset, and prolonged course, with a characteristic train of symptoms which, however, may vary considerably in intensity. Unless terminated by an intercurrent infection, the outcome is usually favorable. Frequently the mother cannot state accurately the time of onset of the disease although in many instances an upper respiratory infection either initiates the symptoms or quickly becomes an associated

TABLE I
FIRST SYMPTOMS OBSERVED BY INFORMANT

SYMPTOMS	NUMBER OF PATIENTS
Fatigue, irritability, anorexia	17
Lacrimation and photophobia	5
Painful and itching extremities	6
Rash (erythema on face and body)	5
Deep muscle pain	3
Pain in abdomen	3
Vomiting	1
Furunculosis	1
Enuresis	1
Convulsions	1
Loss of weight	1
Preceded by acute respiratory infection	12
No acute infection noted preceding onset	32

process. The infant or young child gradually becomes irritable, fretful and sleepless, and refuses food. Cessation of growth and then progressive loss of weight ensue. Profuse sweating, lacrimation and photophobia with excessive secretions from the nose and throat develop. The cheeks are bluish red in color, with the tip of the nose, in many cases, very red. The expression of the suffering patient is worried and unhappy. Ulcerations of the mucous membrane of the mouth are of frequent occurrence. Sooner or later hyperemia alternating with ischemia appears on the hands and feet. The palms and soles develop a dull, beefy red, frost-bitten appearance, and although infants show evidence of marked discomfort and older children complain of intense burning and itching in these locations, the extremities usually feel cold and clammy. Maceration of the skin of the palms and soles occurs followed by desquamation and frequently secondary infection. Rashes of papular type which itch intensely may appear over the whole body. There is, however, a wide variation in the intensity or severity of the cutaneous lesions and it seems quite possible that a patient may suffer from acrodynia and present minimal

skin lesions Falling out of the hair loosening of the teeth, loss of finger and toe nails are frequently observed

The patient tends to assume abnormal positions in bed, frequently placing himself in the knee-chest position with his head burrowed in the pillows This position has been attributed to the photophobia, but, as older children with the disease often complain of abdominal cramps, we are inclined to believe that even infants may assume this position in an attempt to relieve abdominal discomfort

Physical examination reveals fundamental circulatory disturbances early in the disease, often before the appearance on the hands and feet of the typical vascular changes Signs of the circulatory involvement are tachycardia and an elevation of the blood pressure The pulse rate varies usually between 140 and 200 per minute and is little influenced by cry effort or sleep The rhythm is regular The appearance of tachycardia in the early course of the disease is well illustrated by the following case A little girl of five and a half years, who was brought to her physician because of anorexia was found to have a persistent tachycardia without other physical signs of disease Subsequently, after a period of several weeks, the typical manifestations of acrodynia developed Hypertension is present to some degree in all cases and is said by Feer to be the most constant sign of the disease In another of our patients, a boy of seven years, abdominal pain, hypertension and tachycardia preceded by several weeks the appearance of cutaneous manifestations Electrocardiographic tracings show no abnormality other than tachycardia

In addition to the features mentioned above symptoms referable to the central nervous system with profound mental disturbances frequently appear early and persist throughout the course of the disease Lassitude apathy irritability and disturbances of the sleep rhythm together with diminished activity and muscular hypotonia are almost constant findings Muscular pains are complained of and weakness or paralysis of the extremities occur occasionally In one of our patients presenting a typical picture of acrodynia, paralysis of the extremities developed with loss of deep reflexes and persisted for three weeks with thereafter a gradual return to normal function throughout this period sensation in the extremities remained intact It is not unusual for the patients to develop tremors of the extremities and even coma and convulsions We have observed four patients with convulsive episodes.

As mentioned previously evidences of an increased secretory activity become manifest There is excessive lacrimation and rhinorrhea sialorrhea and sudoresis Dehydration evidently is due in addition to the diminished fluid intake to water loss through the skin resulting from the glandular activity

Anorexia, vomiting, and constipation are among the evidences of gastrointestinal disturbance commonly observed in acrodynia. Analysis of the gastric contents in two of our patients showed achlorhydria, there was, however, a normal response of gastric secretion to histamine.

Our analysis did not show with any constancy the elevation of the basal metabolic rate which has been described in the disease. Although the basal metabolic rate was found in one case to be as high as 60 per cent above normal, in other patients dependable determinations of the metabolism showed a normal or even reduced oxygen consumption. The difficulty in establishing basal conditions for the determination of the metabolic rate is obvious in children who are fretful, irritable and suffering from constant pain.

The percentage of sugar in the blood was frequently abnormally high and glucose tolerance tests showed, in five of six cases, curves simulating in some respects those found in patients with diabetes.

The urine of patients in the more severe stages of acrodynia has been usually quite concentrated, probably due to the partial dehydration of the patients. Albumin was found in the urine on one or more occasions in ten of our cases. Glycosuria was even more frequent, occurring in fourteen patients.

Erythrocytosis and leucocytosis were present in the peripheral blood, due probably to the partial dehydration mentioned above. An elevation of the serum protein was found to be present in some cases and absent in others. In one instance the serum protein was reduced to 4.5 gm per cent, although the child had a polycythemia and other evidences of mild dehydration. The failure of the serum protein to be elevated in this and similar cases was thought to be due to the prolonged partial starvation of the patient with considerable destruction of tissue proteins and ultimate reduction in the serum protein.

The inorganic elements of the blood of patients suffering from acrodynia have been depicted as within normal limits, with the exception of the blood calcium which has been reported to be elevated.⁸ Remarkable elevation of the blood calcium was not found in our experience, nor were there reductions below the usual normal figure.

The etiology and pathogenesis of acrodynia remain obscure despite efforts on the part of numerous investigators to cast some light on the subject. Two possible underlying causes of the disease have been suggested, infection and dietary deficiency. Unequivocal supportive evidence for one or the other of these causes was not found in our analysis nor from observations secured by various therapeutic tests. In this connection, however, it is of interest to note the seasonal incidence according to the time of hospitalization of the patients in this series of cases (Fig 1). When the presenting symptoms, the physical signs and the laboratory data are considered carefully, it is apparent that there is present a widespread and fundamental derangement involving

many organs and tissues of the body. Therefore, it does not seem unreasonable, whatever the precipitating cause, to relate certain of the outstanding features of the disease to disturbance of the central nervous system together with a dysfunction of the autonomic nervous system, the latter suggested first by Feer.

Mentioned briefly, the signs which in our opinion are indicative of dysfunction of the autonomic nervous system are dilatation of the pupil and photophobia, rhinorrhea, sialorrhea and sudoresis, vaso motor disturbances of peripheral vessels of the hands and feet, tachycardia and hypotension, alopecia neurotica, spasmodic abdominal pain, hyperglycemia and increased basal metabolic rate.

Inasmuch as contraction of the spleen is brought about through the activity of the sympathetic nervous system splenic enlargement

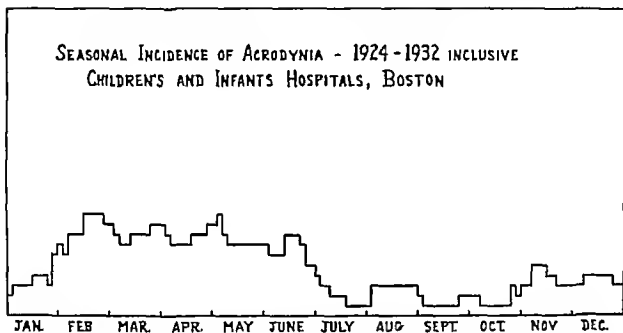


FIG. 1.—This figure is constructed from hospital patient days and represents the summation of the periods of hospitalization of our cases. Obviously the onset of the disease precedes by an indeterminable period the peak shown in the figure.

should be encountered but rarely in a disease characterized by excessive activity of this system. It is interesting to note that in only one of our forty four cases was the spleen enlarged. In this patient the spleen was readily palpable in the early stages of the disease but within a few weeks it became reduced in size so that it could no longer be felt.

In Table II are listed the outstanding symptoms and signs of acrodynia compiled from the literature and confirmed by the analysis of our series of cases. The features of the disease are shown in relation to the known action of various portions of the nervous system. Many of the symptoms and signs suggest definitely a cerebral involvement and others point to a spinal cord or peripheral nerve injury. Numerically, however the manifestations are predominatingly those of a disorder of the autonomic system.

TABLE II

PATHOGENESIS OF THE SYMPTOMS AND SIGNS OF ACRODYNIA

I	Symptoms of cerebral or spinal involvement
	Apathy
	Muscular weakness and paralysis
	Deep muscle pains
II	Symptoms probably cerebral or spinal but possibly due to autonomic involvement
	Hypomotility and hypotonia
	Hyperesthesia
	Coma and convulsions
III	Autonomic involvement
	Sympathetic disturbances (overactivity)
	Vasomotor disturbance (hands and feet, less marked on trunk)
	Dilatation of the pupil and photophobia
	Tachycardia
	Sweating
	Falling of the hair
	Hypertension
	Elevated blood sugar—glycosuria
	Autonomic disturbance, not definitely assignable to sympathetic involvement and possibly due to parasympathetic involvement
	Salivation
	Rhinoorrhea
	Vomiting
	Abdominal pain
	Hypomotility alternating with colicky hypermotility of G. I. tract
	Constipation
	Difficult micturition
IV	Secondary involvement
	Maceration of skin due to profuse sweating
	Secondary infection
	Dehydration due to excessive water loss
	Elevated red cell count
	Elevated serum protein
	Concentrated urine
	Constipation
	Loss of weight
	Negative nitrogen balance

In Fig 2 is shown a chart of the relationship of the autonomic nervous system to the innervation of the organs and tissues of the body. Apparently not only the thoracoabdominal autonomic, the sympathetic system, is involved in acrodynia, but there is also a disturbance of the craniosacral, or parasympathetic system. Inasmuch as the sympathetic and parasympathetic nervous systems have opposing actions in those organs where fibers from both enter into the nerve supply, it is

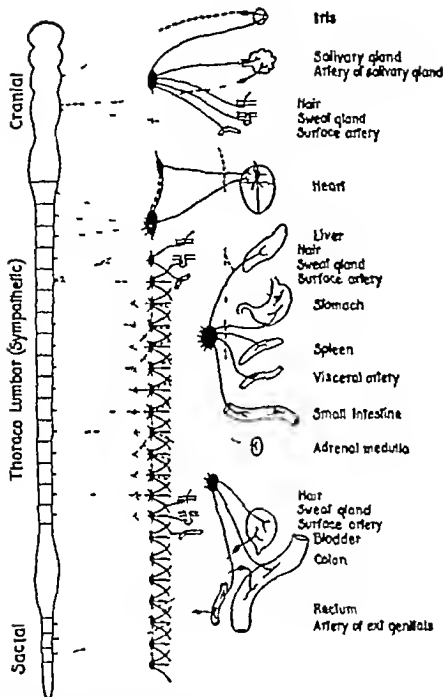


Fig. —Diagram of the general arrangement of the autonomic nervous system.

The brain and spinal cord are represented at the left. The nerves of the somatic system are not shown. The preganglionic fibers are in broken lines, the post ganglionic fibers are in solid lines. The cranial and sacral autonomic systems have limited, sharply directed, nervous discharges to specific organs, while the sympathetic has a diffuse, widespread discharge of impulses by reason of the extensive bridging or connecting fibres overlapping one another and reaching some distance up and down the chain of ganglia.

The outstanding functions of the autonomic nervous system may be listed as follows:

Cranial Autonomic

- 1 depresses and slows the heart.
- 2 constricts bronchi.
- 3 motor to intestine—relaxation of sphincters
- 4 secretory to glands of stomach.
- 5 secretory to parotid gland.
- 6 constriction of pupil.

Sacral

- 1 contraction of muscles of bladder
- 2 erection of penis by relaxing walls.
- 3 motor to large intestine.

Sympathetic

- 1 dilatation of pupil
- 2 secretory to sweat gland
- 3 vaso-constrictors with few dilator fibers to blood vessels.
- 4 acceleration and increased contraction of heart
- 5 dilatation of bronchi.
- 6 inhibition of bladder contraction.
- 7 contraction of bladder sphincter
- 8 contraction of spleen.
- 9 increased conversion of glycogen into glucose in liver

(Figure reproduced through the courtesy of Dr W. B. Cannon, from his book *The Wisdom of the Body* W W Norton and Company Inc. publish. rs.)

manifestly impossible in considering many of the features of acrodynia to determine whether the imbalance of control with the resulting overactivity of an organ is the result of increased stimulus from the one system or diminished and suppressed activity of the opposing system

Finally, certain features of the disease may be considered to be due to alterations in body function entirely secondary to one or another of the underlying disturbances. The manifestations which may be considered secondary have been so listed in Table II

From a study of Table II it becomes apparent that the outstanding features of acrodynia may be attributed to overactivity or unopposed activity of the sympathetic nervous system. Dehydration, partial starvation and secondary infections account for many more of the symptoms observed in the condition. But there still remain a number of manifestations which point definitely to a central nervous system involvement

The number of organs and tissues involved in acrodynia with clinical manifestations referable to a central nervous system disorder together with an extensive involvement of the autonomic nervous system would suggest, if this conception is true, that pathologically there should be found in acrodynia a widespread peripheral lesion involving the sympathetic chains or a central lesion involving particularly the region of the centers of autonomic control, which are presumed to be located in the diencephalon. The central lesion would more satisfactorily explain the complete picture

Clinical pathologic data supporting the conception of a central nervous system involvement are found in examination of the spinal fluid. Early in the course of the disease the spinal fluid has been reported to show an increase in globulin and a pleocytosis.⁹ Spinal fluid examinations were made on one or more occasions in seventeen of our patients. None of these examinations were made at the onset of the disease inasmuch as hospitalization of the patients was not carried out until the process had become quite advanced. Our analysis showed the spinal fluid to be under normal pressure and to be clear and colorless. The cell counts were within normal limits. The globulin was increased as determined by the Pandy test in six of the seventeen cases, and quantitative determination of the total protein yielded values as high as 250 mg per 100 cc of spinal fluid. The sugar was normal in nine cases and appeared to be abnormally high in the remaining eight cases. These findings in the spinal fluid would not indicate the presence in the brain of hemorrhage or gross inflammation. The increase in the total protein, however, might well indicate a mild inflammatory or a degenerative process.

With these possibilities in mind, pathologic changes in acrodynia should be sought in the central nervous system, and in the sympa-

thetic chains. Such searches have not been entirely unrewarded. Degenerative changes in the myelin sheaths of the peripheral nerves have been found by several investigators. However, degenerative changes per se do not indicate the position of fundamental pathologic changes but only that they may be higher up. In fact, degenerative peripheral changes are found in a variety of diseases with central nervous system lesions, among them poliomyelitis and various forms of encephalitis.

Pathologic material secured from patients with acrodynia is not extensive, but various studies, apparently thoroughly made, have shown that in acrodynia, in addition to the degenerative peripheral demyelination, cellular infiltration is present in the spinal cord and in the nerve roots. Byfield early reported degenerative changes in the anterior horns of the spinal cord, edema of the sensory roots and beginning degeneration of the nerves. Paterson and Greenfield¹⁰ refer to cellular infiltration in the spinal cord, with demyelination of the peripheral nerves. Kernohan and Kennedy¹¹ have described extensive demyelination as well as degeneration in the spinal cord extending as high as the base of the brain.

Warthin¹² found in two cases of acrodynia the essential pathological changes to be extreme edema and slight meningeal irritation of the central nervous system, chronic erythema of the skin with hyperkeratosis, hypertrophy of the epidermis and sweat glands with slight pigmentation of the rete, with associated or terminal respiratory infections and gastrointestinal "catarrh and inanition."

Wyllie and Stern¹³ confirmed the finding of diffuse infiltration of the spinal cord described first by Paterson and Greenfield, but were unable to determine the type of infiltrating cells. Chromolysis of the central type was found in the anterior horn and myelin degeneration was observed in the peripheral nerves.

Orton and Bender¹⁴ found chronic lesions in the lateral horns in the thoracic and lumbar regions, loss of nerve cells, with glial replacement. The cells which were lost were the ones which are said to connect the spinal cord with the sympathetic nervous system.

Careful serial sections of the brain stem thus far have yielded slight additional information. De Lange¹⁵ made serial sections of the di- and mesencephalon and found in the regio tuberoinfundibularis both diffuse glial proliferation and small glial nodules. There was no neuronophagia. Here and there in scattered, irregular distribution there was slight glial proliferation in the basal ganglia, thalamus, and dentate nucleus.

From a study of five cases of acrodynia at autopsy we have been unable to demonstrate histopathologic changes which could be considered characteristic or explanatory of the disease. All of the deaths in this series were attributable to severe acute infections, mainly in the upper respiratory tract and lungs. The changes in the other or

gans could be explained largely on the basis of the terminal infection. Examination of the central nervous system, the peripheral nerves and the sympathetic nervous system failed to disclose microscopic changes which could not be related to the terminal infection.

SUMMARY

The data herein reviewed support the suggestion that the manifestations of acrodynia are dependent upon a diffuse disorder of the central nervous system with associated involvement of the autonomic nervous system. The mechanism by which the symptoms and physical signs of acrodynia are produced is, in large measure, traceable to a diffuse stimulation of the autonomic nervous system with involvement and overactivity not only of the sympathetic but also of the parasympathetic divisions of this system.

REFERENCES

- 1 Selter, O. *Arch f Kinderh* 37 468, 1903
- 2 Swift, H. *Lancet*, 1914. *Med J Australia* 1 155, 1921
- 3 Bilderback, J. B. *Northwest Med* 19 263, 1920. *J A M A* 84 495, 1925
- 4 Weston, W. *Arch Pediat* 37 513, 1920. *South M J* 19 665, 1926
- 5 Byfield, A. *Am J Dis Child* 20 347, 1920
- 6 Weber, F. P. *Brit J Derm* 33 228, 1921. *Brit. J Child Dis* 19 17, 1922
- Thursfield, J. H., and Paterson, D. H. *Brit J Child Dis* 19 27, 1922
- 7 Feer, E. *Schweiz. med. Wchnschr.*, 1922. *Erg. d. Inn. Med. u. Kinderh* 24 100, 1923. *Jahrb. f. Kinderh* 108 267, 1925
- 8 Braithwaite, J. V. *Arch Dis Child* 43 1, 1933
- 9 Emerson, P. W. *J A M A* 77 285, 1921
- Van Bogaert, L., Koumans, V., and Sweerts, J. *Rev. franc. de Pédiat.* 4 86, 1928
- 10 Paterson, D., and Greenfield, J. G. *Quart. J. Med.* 17 6, 1923
- 11 Kernohan, J. W., and Kennedy, R. L. *J. Am. J. Dis. Child.* 36 341, 1928
- 12 Warthin, A. S. *Arch. Path. & Lab. Med.* 1 64, 1926
- 13 Wyllie, W. G., and Stern, R. O. *Arch. Dis. Child.* 6 137, 1931
- 14 Orton, J. T., and Bender, L. *Bull. Neur. Inst., N. Y.* 1 506, 1931
- 15 De Lange, C. *Jahrb. f. Kinderh* 86 193, 1932

THE RÔLE OF ERYTHROCYTE FRAGMENTATION IN THE GENESIS OF ANEMIA

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FRAGMENTATION with ultimate disposal of the fragments by phagocytes of endothelial origin, has long been recognized as the normal method of disposal of the red cell. Ehrlich, as long ago as 1880, described the process in some detail, recognizing the poikilocyte as a cell preparing for dissolution and designating the free motile fragments seen in fresh preparations as schizocytes. A number of other observers commented on evidences of fragmentation seen in normal blood and the common assumption seems to have been that these fragments grow smaller and smaller through the mechanical effects of attrition in the circulation, to become a sort of hemoglobin containing dust whose final disposition is a function of reticuloendothelium in various sites. Roux and Robertson in 1917 published observations which went to prove that fragmentation is a constant feature of the blood of normal animals. Roux in 1923 reviewed the whole literature of the normal fate of the red cell and Doan and Sabin in 1926 gave a rather more complete description than any of the others of the fragmentation as seen in rabbits' blood, with observations also on ultimate phagocytosis of the fragments by desquamated endothelial cells in the blood stream.

From these studies we obtain a very satisfactory picture of what happens to the senile red cell up to the final, still little understood process of bilirubin formation and reutilization or deposition of the iron. The fragmentation process is best studied in the fresh moist preparation unstained or made with a film of neutral red sealed with a mixture of vaseline and paraffin and watched in the warm box whose temperature should be kept below 37°, as above this point increases in temperature have been observed to cause acceleration of the process (Isaacs Doan and Sabin and others). We can offer no better description of what is to be seen in the sealed film of normal blood than that of Doan and Sabin, which we quote: "In watching fragmentation we have found that a red cell puts out a long process and thereby becomes the so-called poikilocyte. At first the process does not move then it begins to vibrate slowly then faster and faster. This vibration marks the beginning of fragmentation. As the process vibrates it gradually becomes thinner and thinner at some point and then separates. If the thinned out place is at the end of the long process the fragment becomes a rod often looking like an irregu-

lar but yellow bacillus, if near the tip, it becomes a round or oval body. We have seen every variation in size and shape of these processes, up to an actual division of a red cell into two equal parts. Sometimes two or more processes form on a red cell at the same time." We would add to this an observation of our own, made also by Ehrlich, that many of the small slender fragments, which are likely to have a refractile enlargement at one end, and to show a resemblance to spermatozoa, have definite independent motion, so that in the pathologic states to be described, in which the drop of blood is full of the fragments, one might easily think that he was observing the blood of some protozoan infection. It is, of course, to be understood that in normal blood comparatively few cells undergo disintegration at the same time, so that some search is necessary to find the fragmenting forms. We have found "budding" a convenient term for these cells that are putting out processes preparatory to fragmentation.

Considering that it has been generally, if rather vaguely recognized that fragmentation plays the most important part in the normal destruction of the red cell, it seems surprising that so little attention has been given to the likelihood of abnormal increase in this process as a factor in the genesis of anemia. It is common enough to speak of "increased blood destruction" in certain types of anemia, but this increased destruction is more often a deduction from increased pigment metabolism, or from lack of other adequate explanation for the anemia than a direct observation, and the assumption is often made that increased destruction and "hemolysis" are synonymous terms. Hemolysis should mean the freeing of the pigment from the red cell, as it may be observed *in vitro* as the result of certain immune reactions, exposure to chemical or bacterial poisons, or to changes in osmotic pressure, as in the fragility test. *In vivo* such processes are rare. They are to be met with in paroxysmal hemoglobinuria, in transfusion reactions and in some kinds of poisoning. The type of the so called hemolytic anemias is hemolytic icterus, in which the cells, which have a peculiar susceptibility, apparently collect in the spleen and lose their pigment there by a process not clearly understood, but which is not preceded by fragmentation in the blood stream. Erythroblastosis fetalis probably involves a similar process. Some of the anemias often spoken of as hemolytic, however, including pernicious anemia, erythroblastic anemia, perhaps sickle cell anemia and the hemolytic anemia of pregnancy, probably do not belong in this class. Hemolysis as observed *in vitro* involves the passing of the hemoglobin into solution in the fluid menstruum, with the cell form remaining as a "ghost." The breaking of the cell into pieces which retain their hemoglobin evidently should not be confused with this, even though hemolysis must be the ultimate fate of this hemoglobin.

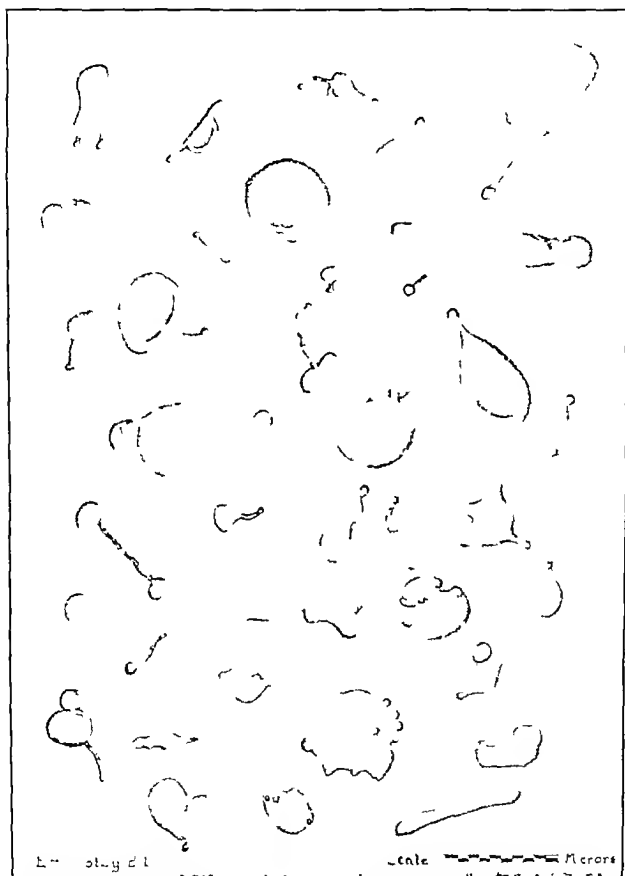


FIG. 1.—Fragments and forms of cells about to break up as seen in the sealed fresh film.

Our attention was first called to the clinical significance of excessive fragmentation in the case of a four-year-old girl admitted to the Children's Hospital in November, 1932, because of jaundice, ascites and splenomegaly which had developed in the course of chronic suppurative otitis media. Splenectomy was necessary, and the spleen showed an extreme degree of chronic infectious splenitis. The jaundice and ascites disappeared after the operation and have not returned.

The patient was not anemic on admission, having 13.5 gm Hgb and 4,600,000 RBC. There was, however, evidence of considerable disturbance in erythropoiesis, with anisocytosis and poikilocytosis, many microcytes, and 10 per cent reticulocytes. Resistance to hemolysis was somewhat increased, and the curve of gastric acidity was normal. Quite exhaustive laboratory studies gave no other significant findings.

The child did well until, in the course of convalescence, suppuration developed in the operation wound and in a needle puncture. This was followed by a rapid fall in hemoglobin and erythrocyte count, which soon produced a state of grave anemia. Studying the blood at this stage, Lee was struck by the numbers of peculiarly shaped erythrocytes, whose development she thought would be better observed in moist preparations. These were made, and presented a remarkable picture. The whole film was alive with motile, hemoglobin-containing fragments, the commonest being the spermatozoon-like forms already mentioned. A large proportion of all the red cells showed some one of the forms of distortion described by Doan and Sabin as preparatory for fragmentation, either the poikilocyte with the waving tip, the slender processes, single or multiple, or the nearly median fission, the latter being obviously the cause of the many microcytes to be seen in the film. It was evident that a large proportion of the erythrocytes were being destroyed at the same time, and that regeneration was not keeping pace with this process, as few young forms were to be found. This destruction was not due to any toxic property of the serum, as cells from a normal person mixed with the patient's serum were not affected, nor did the patient's cells disintegrate less rapidly in normal serum. After a few days' study of these phenomena transfusion became necessary. Other therapy was not employed as it was desired to observe the behavior of the transfused cells. The immediate effect of transfusion was striking. The child, previously prostrated and apathetic, revived immediately, and was happy and playful. The transfused cells were evidently not affected by the fragmentation process, as the proportion of distorted cells was greatly diminished and remained so for more than two weeks, as might have been expected from the normal life of the transfused cells, with the patient's cells undergoing destruction as before. Our observations were interrupted at this point by an attack of

measles. On her return two weeks later she had only 25 gm Hgb, with no important change in the rest of her blood picture except that there were 900,000 platelets and 17 per cent normoblasts. Reticulocytes were absent. Fragmentation was again extreme. Transfusion was followed by the same response as before.

We have observed this sequence of events in this patient after four transfusions. Each time there has been the same prompt improvement, with marked diminution of degenerating cells, which lasts between two and three weeks, after which the great excess of fragmenting cells is again apparent. In all this time there have been practically no reticulocytes in the blood. The platelet count reached the maximum of 900,000 four months after the splenectomy, then fell quite rapidly to the pre-operation level of 250,000. It did not appear to have any relation to the number of fragments in the blood. The patient has had during the period of observation operations upon both mastoids and a tonsillectomy. She had received liver iron and copper for three weeks before the fifth (recent) transfusion without apparent effect upon the blood. Since this transfusion and the tonsillectomy which followed it, reticulocytes have reappeared in a proportion of 10 per cent.

We are satisfied that this whole disease picture has resulted from the toxemia of focal infection. The excessive fragmentation was probably beginning when she was admitted, but was compensated by increased production until the wound infections added the final insult to the marrow. Since that time we have had a picture of hypoplasia of erythropoietic marrow plus greatly increased destruction by fragmentation. Our observations of the process of disintegration in the moist films and of the effects of transfusion have aided us greatly in understanding the genesis of the anemia. The splenomegaly had no causative part, but the splenectomy doubtless made the fragments more prominent in the blood stream through lessened phagocytosis. Therapy if successful at all in such a case will probably help only after the patient is free of her various infections.

Three patients with erythroblastic anemia, two of them sisters, all of whom have had their spleens removed, have been studied during this same period. This anemia is characterized by extreme hyperplasia of erythropoietic marrow and a constant outpouring of young and immature cells into the circulation, with very high counts of reticulocytes and erythroblasts. Increased pigmentation of the serum indicates abnormal destruction, which we had supposed to be due to hemolysis of some type in spite of increased resistance to hypotonic solutions until we studied moist films from these patients. They show the most extreme fragmentation that we have observed, even when the hemoglobin and red cell levels are practically stationary. The balance is, of course, due to the great increase in erythropoiesis. The

fragmenting cells show all the forms previously described, and in addition many which look as though they had been burst by an explosion. We have on various occasions tested serum from patients with this disease against normal cells without seeing any destructive effect. The great splenic enlargement is probably "spodogenous," and has nothing to do with causing the anemia.

A boy of eight and one-half years, with a hypochromic, hypochlorhydric anemia said to have existed from infancy, gave interesting findings. From the appearance of stained smears his anemia would have been termed microcytic. Fresh films gave a different impression. There was decided excess of fragmentation, but of a somewhat different type from that observed in the first case, with fewer poikilocytes and "budding" cells, and a notable proportion of long elliptical cells resembling forms seen in sickle cell anemia. These and many of the normal-sized round cells tended to divide by median fission, producing microcytes. Our impression was that most if not all of the microcytes were produced in this way, and that the anemia could not be called microcytic in the sense that the small cells were produced by the marrow. This blood was studied in an overheated box. Under this condition the process of fission could be seen to go on in a cell until there was a group of five or more minute round forms in the place of the original cell. Ponder in his book describes precisely such an appearance as an evidence of hemolysis. If he were right, there should be a ghost cell remaining, which we did not see. There were less of the small fragments in this blood than in the bloods of the splenectomized patients, presumably because this boy's spleen was functioning.

These were unusual types of anemia. In attempting to estimate the general importance of fragmentation as a factor in producing anemia we have studied films from a number of the more ordinary forms. This group has included (1) Three cases of the combination of deficient or improper feeding and infection so frequently seen in the polyclinic. They showed fairly severe anemias of the type analyzed last year by Josephs, in which he demonstrated increased destruction by determination of pigment excretion. Hypoplasia of the erythropoietic marrow is unquestionably present in cases of this type. In all these we were able to observe marked increase in the percentage of fragmenting forms, though the small fragments, more frequent than in normal blood, were not nearly so much in evidence as in the blood of the splenectomized patients. (2) Two infants with streptococcus septicemia. In one, with hepatitis and jaundice, but little anemia, we could not detect increased fragmentation, in the other, without jaundice but more anemic, it was definite. (3) Three cases of pneumonia. In two, with moderate anemia, we could not definitely see an increase in fragmenting forms, in the third, a more anemic

infant in whom malnutrition had probably played a part, it was very distinct (4) A severe anemia in a three months old infant of the type which we have described elsewhere as due chiefly to deficient iron reserve, with the acute development precipitated by infection. This blood showed many misshapen forms but few small fragments. Within a few days after a transfusion all signs of cell destruction had disappeared. In the cases which responded with moderate rapidity to medical treatment signs of fragmentation progressively diminished but this did not always seem to keep pace with the clinical improvement, nor was there any obvious relationship between the appearance of reticulocytes and the disappearance of fragmentation.

Recently we have had in the hospital two sisters with congenital hemolytic icterus. One came in just after a hemolytic crisis, and the second was admitted during a crisis in which her hemoglobin fell from 15 gm to 6 gm within ten days. Neither of these patients showed any sign whatever of cell disintegration in the circulating blood. It was noticeable that the moist films seemed to show less microcytosis than the stained smears, also that there were no poikilocytes in stained preparations.

DISCUSSION

Study of the red cells in fresh sealed preparations was once a common procedure. Of recent years staining methods have almost entirely supplanted it except in the diagnosis of sickle cell anemia, and in the "supravital" technique. Our studies on these cases have led us to believe that it still has a very definite place in the appreciation of the mechanism of anemia. We have made use of the warm box at temperatures varying from 32° to 37° but it is not really necessary except for prolonged observation as the phenomena are readily observed at room temperature.

Our studies made in this way have satisfied us that in the ordinary secondary anemias and some of the primary forms blood destruction by an exaggeration of the normal process of fragmentation is a definite, easily observed feature, usually accompanied by indications of marrow hypoplasia in that regenerative forms are lacking. We have not arrived at a quantitative method of measuring fragmentation or the steps leading to it, but the difference between what is to be seen in normal blood and the appearance in a pronounced anemia are so marked that it is not difficult with a little experience to arrive at a fairly satisfactory standard of comparison.

The reason for this destruction is not perfectly clear. The natural assumption would be that the red cells which go to pieces so easily do so because of imperfect structure. Another possibility has occurred to us. If one thinks of the emergence of the cell into the circulation as a result of the push of new cells forming behind it, it might be

supposed that in a hypoplastic state the cells remain a longer time in the marrow, and are already old when they emerge. This obviously could not be the explanation of the destruction in erythroblastic anemia, in which an excessive output of young cells is a prominent feature. There is no good explanation of the abnormal fragmentation in this disease except defective structure. If the idea of old cells coming into the circulation in the hypoplastic states were accepted, it would explain such observations as the lack of marked increase of fragmentation in the early stage of the anemia, and its continuance after improvement has begun.

The two cases of hemolytic icterus, as has been pointed out, give an entirely different appearance in the moist films. There is no indication here of fragmentation, and the microcytes, which are an important characteristic, are probably formed as such in the marrow, not the result of division in the blood stream. Poikilocytosis, which we believe to be evidence of fragmentation, is not, in our experience, met with in hemolytic icterus, although we have seen it noted in case reports. It is not impossible that in some cases both means of destruction might be at work, and this might explain the occasional failure of splenectomy.

We have had recently no case of sickle cell anemia in which the process was active. These cells would be difficult to study for fragmentation because of the rapid "sickling." This is generally assumed to be a hemolytic disorder, largely because of its resemblance in some features to hemolytic icterus. We are inclined to think that the resemblance to erythroblastic anemia is closer, and are not convinced that the disease belongs in the hemolytic group. This question might be settled by study of an appropriate case, especially after splenectomy*.

Study of fragmentation might seem to have some bearing on the theory of the origin of platelets from the red cells, recently revived by Watson. Without entering into this discussion, it seems worth while to record the observation that in only one of the cases in which we have observed an unusual amount of fragmentation was there a platelet count above the average.

We have thought, too, that the appearance of these fragments is not consistent with some of the theories of red cell structure. All of the fragments large enough to study retain the typical hemoglobin color. As they are evidently pieces of cell membrane, the hemoglobin must be firmly attached to it. Pepper and Farley have advanced a similar argument.

*Since the above was written we have had opportunity to see the blood of a patient with sickle cell anemia whose spleen was removed about two years ago. Her hemoglobin has remained close to 8 gm for some time. This blood is like that of erythroblastic anemia in having many budding forms and small fragments though the picture is not an extreme one. There is here also a high percentage of reticulocytes.

We are presenting these studies in the hope that others may be induced to make the moist film a part of their routine of blood investigation, as we believe that valuable information regarding the pathogenesis of the suemias is to be gained in this way.

REFERENCES

- Doan and Sabin J Exp Med 43 839 1926
 Ehrlich Farbanalytische Untersuchungen zur Histologie und Klinik des Blutes,
 Hirschwald, Berlin 1891.
 Isaacs, Brock and Minot J Clin. Invest. 1 4-5, 1925
 Josephus Bull. Johns Hopkins Hosp 51 18, 1932.
 Oliver Science 40 645
 Ponder The Erythrocyte and the Action of Simple Hemolysins, London 1924
 Oliver and Boyd.
 Rous Physiol. Rev 3 75 1923
 Rous and Robertson J Exper Med 25 631 and 640 1917
 Watson Edinburgh M J 39 220 1932.

PEDIATRICS—WHAT IS IT?

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PEDIATRICS is not a specialty comparable to surgery, neurology, and orthopedics, but is instead general practice limited to the care of children from birth, or even before birth, to the age of fourteen years. In the care of children, the prevention of disease is more important than its diagnosis and treatment. There is a closer relationship between general practice and pediatrics than between the latter and the other specialties, because many physicians in general practice spend a large proportion of their time in pediatrics. Bass¹ recorded that over 20 per cent of the daily work of one hundred and fifty physicians in general practice was with children, and the experience of others has shown that as high as 60 per cent of family practice is in the age group below fifteen years. As Grulee² expressed it, pediatrics is separated from internal medicine by a horizontal line rather than a vertical one.

Pediatrics has five important overlapping functions, largely preventive, and most physicians are interested in them to different degrees. (1) The care of the newly born, with recognition of jaundice, bleeding, malformations, etc., (2) feeding, and diet regulation, nutrition, periodic examinations, the training of infants and children in health habits, etc., (3) immunization against diphtheria, smallpox, etc., as well as the prophylaxis of scurvy, pellagra, rickets and tetany, (4) the recognition of ill children (this probably is one of the most neglected features of pediatrics), and (5) the diagnosis, prognosis and treatment of children's diseases, especially during their early and curable stages.

Infant mortality in this country is higher than it should be. There are two alternative methods of reducing it, (a) the prevention of every condition possible, and the diagnosis and treatment of all other diseases, or (b) the focusing of attention and efforts on the most serious conditions. The first, though ideal, is impractical, for it is neither possible as physicians to be omniscient, nor as medical teachers to instil complete knowledge in medical students. In this day and time, medical students and physicians, because of the accumulation of scientific details, must learn less and less about more and more, and consequently are being forced further and further away from the goal of complete knowledge. However, it is possible to concentrate ma-

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for efforts on the narrower field of serious conditions in which the greatest good can be accomplished so that, knowing the incidence of disease, the evaluation of symptoms, and a clinical study of the individual patient can be stressed.

Unfortunately, there is no agreement in regard to the most serious conditions in children. Osler³ once said "Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you." A clinical knowledge of tuberculosis was held in equally high regard. Today, however, the picture is changed, and from a teaching point of view, it probably is wiser to emphasize that Wassermann reactions and intradermal tuberculin tests are much more important than are the clinical symptoms of syphilis and tuberculosis in children. A Wassermann test should be done on every child examined, regardless of clinical or social condition, and not only on those children suspected of having syphilis. Certainly for every case of syphilis in children diagnosed by clinical signs, five are discovered by routine Wassermann tests. An intradermal tuberculin test which is negative, with rare exceptions, will eliminate the possibility of tuberculosis, while if it is positive, the taking of the temperature night and morning usually will demonstrate, in most cases, whether the disease process is active or quiescent. Stewart⁴ has stated that in the discovering of childhood tuberculosis if a value of 100 per cent is assigned to the intradermal tuberculin test as a measure of its efficiency, the roentgen examination has a reliability of about 25 per cent, while a physical examination has an efficiency of a small fraction of 1 per cent. Of course it is popular in 1933 to criticize such statements as the foregoing, on the basis that more time should be spent studying clinical symptoms and less reliance placed on laboratories. However the methods which are scorned today as too scientific and nonclinical are likely to be the accepted clinical techniques of future generations. To wit the stethoscope, which now is regarded as the keystone of bedside medicine was ridiculed when Laennec introduced it in 1819. As late as 1840 Samuel Chew a preceptor protested that "medical auscultation is wholly useless and I can investigate diseases of the chest without that mode of examination better than any one else can with the help of a cartload of stethoscopes."⁵

Nevertheless notwithstanding the complexity of the situation some progress toward a decision as to the most important pediatric conditions can be made by classifying these diseases in at least three ways: (1) By determining their relative incidence from outpatient and hospital records; (2) by discovering their relative severity through a study of mortality rates, and (3) by arranging them on the basis of those which are preventable by antenatal, natal, and postnatal meas-

ures, those amenable to specific therapy, and the remainder which, at present, cannot be prevented or cured

The relative frequency of children's diseases has been demonstrated by Arena and Harriss,⁶ who found in 150,539 cases of 346 different

TABLE I
RELATIVE FREQUENCY OF DISEASES AMONG 80,000 OUTPATIENT AND HOSPITAL CHILDREN⁶

FREQUENCY (CASES OF EACH DISEASE)	NUMBER OF DIFFER- ENT DISEASES
Over 200 (seen at least once per month)	86 (25%)
101 to 200 (seen every other month)	23 (7%)
26 to 100 (seen twice per year)	65 (18%)
5 to 25 (seen once per year)	89 (26%)
0 to 4 (seen every five years)	83 (24%)
Total cases 150,539	346 (100%)

TABLE II
FIVE PRINCIPAL CAUSES OF DEATH IN EACH AGE GROUP (U S REGISTRATION STATES, 1926)⁷

AGES →	UNDER 1 YR	1 YR.	2 YR.	3 YR.	4 YR.	5 TO 9 YR.	10 TO 14 YR.
Total deaths, all causes	159,411	31,609	14,144	9153	7018	22,779	17,263
CAUSE	PERCENTAGE OF DEATHS IN EACH AGE GROUP						
I. Intestinal diseases (Diarrhea and enteritis)	13	20	11	7			8
II Chest diseases (Pneumonia and influenza)	18	32	27	21	17	13	11
III Heart disease						6	10
IV Accidents		6	11	16	19	22	21
V Infectious diseases Whooping cough Measles Diphtheria Tuberculosis	3	8 8	8 8	6 11	5 12 5	9 6	10
VI Miscellaneous Malformations and causes associated with early infancy Ill defined group	46 4						
Summary of percentage of deaths due to five principal causes in each age group	84	74	65	61	58	56	60

diseases among 80,000 children admitted to the outpatient department and wards of a large children's hospital over a period of twenty years, that eighty-six diseases were common enough to occur at least once per month, and that twenty-three additional diseases were seen on an average of every other month, and that the remaining two hundred and thirty-seven occurred less than twice per year (Table I)

However, it is difficult to be constantly on the alert for even eighty six diseases, not to mention three hundred and forty six

The second method of classification of pediatric disease is based upon the death rate, and directs its emphasis upon the number of deaths which each condition causes, as shown in Table II. The first or intestinal group consists largely of diarrhea and dysentery (enteritis), which, fortunately, are readily diagnosed and usually adequately treated. However, practically all of these cases could have been prevented if the infants had been fed whole lactic acid milk and had been kept in sanitary and fly free surroundings. In the second or chest group empyema probably is the most important cause of death because at autopsy, pus can be found in the pleural cavities of a large percentage of children who have had pneumonia. Early diagnosis of this complication and its adequate surgical treatment might have prevented many of these deaths. Repeated needling and fluoroscopic and x ray examinations are essential in the search for empyema after

TABLE III

PRINCIPAL CAUSES OF DEATH IN A LARGE CHILDREN'S HOSPITAL*

CAUSE OF DEATH	NUMBER OF DEATHS
I Intestinal disease (Chiefly dysentery and diarrhea)	53 (23%)
II. Chest diseases (Pneumonia and empyema)	44 (20%)
III. Heart disease	10 (4%)
IV Neurological diseases (Chiefly meningitis)	52 (22%)
V Miscellaneous	70 (31%)
Total	229 (100%)

pneumonia. The third group of heart disease is more important from the prognostic point of view than from the therapeutic. One occasionally hears of physicians who cure heart disease but up to the present, alleviation of symptoms and attempts to prevent further damage are the best that can be done. The fourth group of accidents is increasing rapidly in importance because of automobiles. Every child must be instructed in caution. The fifth or infectious disease group should not occur at all, for these diseases are preventable. As can be seen from the summary of Table II, those five groups account for 34 to 74 per cent of the deaths in each age group of children.

Arrangement of the 229 deaths for the year 1931 at the Harriet Lane Home (Table III) presents a slightly different picture of the most dangerous diseases. Three of the five groups mentioned above are the same, namely intestinal, chest and heart diseases, but deaths from infectious diseases and accidents do not appear because they were reported among patients admitted to other departments. The most interesting difference shown by Table III is in the number of deaths from meningitis. The explanation probably is twofold, first,

because many very ill patients suffering from this disease are sent to the Harriet Lane Home, and second, because in statistics gathered from the whole country (Table II), a number of deaths really resulting from meningitis are not recognized, nor reported as such. Meningococcus meningitis, a curable disease, forms one-fifth of group IV.

TABLE IV
COMPARISON OF THE CAUSES OF DEATH FROM ALL CAUSES BY AGE IN CHILDREN UNDER FIFTEEN YEARS*

AGE	UNDER FIFTEEN YEARS (PER CENTAGE OF TOTAL DEATHS)	UNDER FIVE YEARS (PER CENTAGE)	FIVE TO NINE YEARS (PER CENTAGE)	TEN TO FIFTEEN YEARS (PER CENTAGE)
I Epidemic and infectious diseases including tuberculosis (Tuberculosis from all causes, included in I)	19 (3)	17 (2) (1% under 1 yr)	33 (5)	28 (10)
II General diseases not included in I	3	2	5	7
III Diseases of nervous system and special sense organs	3	3	6	6
IV Diseases of circulatory system	2	1	6	11
V Diseases of the respiratory system	14	15	9	7
VI Diseases of the digestive system	15	16	13	13
VII Nonvenereal diseases of the genitourinary system	1	1	2	3
XI Malformations	6	7	1	1
XII Early infancy	25	29	—	—
XIV External causes, accidents, etc	7	4	23	22
XV Ill defined causes, and IX Diseases of the skin, and X, Bones (IX and X were each less than 0.25%, VIII, Puerperal state, and XIII, Old age, do not fall in these age groups)	4	5	2	2
Total	240,661 (100%)	199,507 (100%)	23,389 (100%)	17,765 (100%)
Percentage of total by age	100	84 (61% in 1st yr)	9	7

*Deaths (exclusive of stillbirths) from each cause by age in the registration area and each registration state 1927. Mortality Statistics 1927 Part I Tables and General Tables Bureau of the Census U. S. Department of Commerce U. S. Government Printing Office, 1929. (Note: All of the deaths from bacillary dysentery and enteritis are counted as dysentery because experience has demonstrated that dysentery bacilli are responsible for the majority of these deaths. Half of the deaths from bronchopneumonia, lobar pneumonia, and pneumonia, unspecified have been counted as empyema for at autopsy many of the children have empyema which usually has not been recognized. All of the deaths from rheumatic fever, chorea, pericarditis, endocarditis and myocarditis have been grouped as practically all of them are due to infection with the so-called rheumatic virus.)

in Table III The fifth or miscellaneous group contains deaths from syphilis and prematurity which might not have occurred, had antenatal and postnatal treatment of the mother and child by the attending physician been adequate

Table IV, based on the mortality statistics of 1927, confirms the facts recorded in Tables II and III, and also emphasizes the need of more and better preventive pediatrics, because it demonstrates that five groups of diseases and conditions are responsible for 80 per cent of all the deaths in children under fifteen years of age, namely, I—epidemic diseases (19%) V—respiratory diseases (14%), VI—digestive diseases (15%), XII—diseases of early infancy (25%), and XIV—external causes (7%) Most of the diseases and conditions in these five groups are curable if recognized early, and many of them are preventable The most emphasis should be placed on the prevention, recognition and treatment of the diseases and conditions which occur in pre-school children, and especially should antenatal and natal care be stressed, because 61 per cent of the deaths in children occur during the first year of life, and most of them are in early infancy The need for precautions against tuberculous infection and for its early diagnosis and adequate care also is demonstrated by Table IV because deaths from tuberculosis increase in the older age groups, from 1 per cent of the deaths under one year to 2 per cent of those under five years, 5 per cent of those from five to nine years and to 10 per cent of those from ten to fourteen years However the picture is not altogether true for the great number of deaths from all causes in early infancy produces a misleadingly low percentage of deaths from tuberculosis

According to the third method of classification the diseases among children can be arranged in five subgroups (A) those preventable by antenatal and natal measures (birth injuries conditions of early infancy, gonorrheal ophthalmia premature and stillbirths and syphilis), (B) those preventable by postnatal measures (accidents, anemia, dietary deficiencies (pellagra rickets scurvy, and tetany) diphtheria, dysentery (bacillary), malaria malnutrition, measles, pertussis, poisoning rabies, scarlet fever smallpox tetanus tuberculosis, and typhoid paratyphoid fever) and (C) conditions amenable to specific therapy (abscesses, allergy bronchitis convulsions, diabetes, dietary deficiencies diphtheria epilepsy erysipelas, fungus infections lung abscess malaria, meningitis, otitis media, parasites (intestinal) syphilis thymus enlargement and tuberculosis) To this last group should be added such surgical conditions as appendicitis, empyema intestinal obstruction intussusception mastoiditis, and pyloric stenosis Every physician and pediatrician should be on guard constantly that these conditions are not overlooked. The last two subgroups are (D) all other epidemic and infectious diseases, some of which can be

TABLE V
COMPARISON OF THE PREVENTABLE, CURABLE AND NONPREVENTABLE DEATHS BY AGE, IN CHILDREN UNDER FIFTEEN YEARS

AGE →	UNDER 15 YR. (PER CENT)	UNDER 1 YR. (PER CENT)	1 YR. (PER CENT)	2 YR. (PER CENT)	3 YR. (PER CENT)	4 YR. (PER CENT)	UNDER 5 YR. (PER CENT)	5 TO 9 YR. (PER CENT)	10 TO 14 YR. (PER CENT)
A Antenatal and natal preventable causes	26	42	1	1	1	1	31	1	1
B Postnatal preventable causes	27	18	46	42	42	42	25	37	29
C Causes curable by specific therapy	21	9	14	14	13	13	10	17	20
D All other epidemic and infectious causes, some of which can be eliminated by public health and sanitary measures	3	3	6	6	6	6	4	6	5
Total preventable and curable diseases and conditions	77	72	67	63	62	62	70	61	55
E All other diseases which at present cannot be prevented or cured by specific measures	23	28	33	37	38	38	30	39	45
All diseases and conditions	240,661 (100%)	147,134 (100%)	24,405 (100%)	12,256 (100%)	8,322 (100%)	6,890 (100%)	199,507 (100%)	23,389 (100%)	17,765 (100%)

eliminated by public health and sanitary measures (mumps, influenza, poliomyelitis, etc.) and (E) all other diseases and conditions most of which, at present cannot be prevented or cured by specific therapy (encephalitis, leukemia, malformations, etc.)

This third type of classification is an ideal one because it stresses the preventive aspect of pediatrics, a phase which cannot be too strongly emphasized because as shown in Table V 77 per cent of all the deaths among children in 1927 were due to diseases and conditions which might have been prevented or cured. One quarter of the conditions which kill 240,661 children annually (Table V) can be prevented by antenatal and natal measures, one quarter by postnatal means, and one fifth can be cured by specific therapy. An example of what can be done by antenatal care is Geugenbach's⁸ report that the infant mortality was 178 per 1,000 live births from mothers who did not make antepartum visits to their physicians, and only fifteen from those who made nine or more visits. An encouraging study of the benefit of postnatal measures is that of Brooks¹⁰ who recorded that the infant mortality among the colored infants of a Southern city fell

TABLE VI

COMPARISON OF THE PREVENTABLE, CURABLE AND NONPREVENTABLE CAUSES OF DEATH IN A LARGE CHILDREN'S HOSPITAL

CAUSES OF DEATH	NUMBER OF DEATHS
A. Antenatal and natal preventable causes	38 (17%)
B. Postnatal preventable causes	84 (36%)
C. Curable causes	26 (11%)
Total preventable and curable diseases	148 (64%)
E. Nonpreventable diseases	81 (36%)
All diseases and conditions	229 (100%)

from 196 to 119, and that of the white infants from 83 to 57 during the four years in which the visits to the well baby clinics rose from zero to 3,380.

The facts emphasizing the need of preventive measures and early diagnosis and adequate treatment of pediatric conditions can be seen perhaps more clearly by studying an analysis (Table VI) of the 229 deaths which occurred among the 1,052 children admitted to the Harriet Lane Home. Over 50 per cent of these deaths could have been prevented if prophylactic measures had been used by the family pediatrician or general practitioner, and part of an additional 11 per cent might have been averted if a diagnosis had been made earlier and the children sent to the hospital before specific therapy was too late. The figures in Table VII, compiled from one thousand autopsies,¹¹ are not so striking, but they do demonstrate that nearly half of these deaths were from preventable and from curable causes.

The need for focussing attention on the diseases which can be prevented or cured by specific therapy is shown in Table VIII, compiled

from the figures of Arena and Harris⁶ Eighty-two per cent of the 150,539 cases might have been prevented, or the patients cured, while only 62 per cent of the three hundred and forty-six diseases themselves are preventable or curable In other words, as shown in Table IX,

TABLE VII

THE CAUSES OF DEATH IN 1,000 CONSECUTIVE AUTOPSIES IN CHILDREN UNDER FOUR TEEN YEARS OF AGE¹¹

CAUSES	NUMBER
<i>A Antenatal and Natal Preventable Causes</i>	
Syphilis	20
Prematurity	23
Cerebral hemorrhage	12
A Subtotal	55 (5%)
<i>B Postnatal Preventable Causes</i>	
Tuberculosis	96
Gastroenteritis	25
Dysentery	8
Intoxication	70
Marasmus	37
Contagious diseases	47
Accidents	8
B Subtotal	291 (29%)
<i>C Causes Curable by Specific Therapy</i>	
Empyema	20
Meningitis, purulent	64
Mastoiditis	30
Surgery	10
Intussusception	11
C Subtotal	135 (13%)
Subtotal of Preventable and Curable Causes	481 (48%)
<i>E Causes Not Preventable, or Curable by Specific Therapy</i>	
Pneumonia	157
Septicemia	83
Congenital malformation	90
Heart disease (acquired)	42
Atelectasis	8
Status lymphaticus	15
Neoplasms	17
Peritonitis	33
Nephritis	15
Encephalitis	7
Diseases of the blood	11
Miscellaneous	25
Undetermined	26
E Subtotal	519 (52%)
Total	1,000 (100%)

the incidence of cases is higher in the preventable and curable group For example, among 43 per cent of the preventable and curable diseases, the frequency was over one hundred cases per disease, while only 13 per cent of the diseases which cannot be prevented or cured by specific measures had this high incidence

In order that one may arrive at a decision as to the most important disease, they have been arranged in Table X from all three stand-

points (1) Relative incidence, (2) relative mortality, and (3) preventability or curability. Fortunately there is no correlation between the frequency and the mortality of disease for example, abscesses are the most common condition in children, but they are only forty fourth in relative mortality. As a general rule the diseases in children for which medical aid is most frequently sought, do not endanger life. However it is rather humiliating to us in the medical profession that the diseases which cause three-quarters of the deaths in children

TABLE VIII

A COMPARISON OF THE NUMBER OF CASES AND THE NUMBER OF DISEASES AMONG OTHER CONDITIONS AMONG 80 000 OUTPATIENT AND HOSPITAL CHILDREN*

CAUSES	NUMBER OF CASES	NUMBER OF DISEASES
A Antenatal and natal preventable causes	8,550 (2%)	9 (8%)
B Postnatal preventable causes	44,626 (80%)	38 (9%)
C Causes curable by specific therapy	72,007 (40%)	103 (47%)
D Causes preventable by public health measures	1,216 (1%)	0 (8%)
E. All other causes most of which are not preventable, or curable by specific therapy	28 150 (18%)	132 (38%)
Total	150 639 (100%)	846 (100%)

TABLE IX

COMPARISON OF THE FREQUENCY OF PREVENTABLE AND CURABLE DISEASES WITH ALL OTHER CONDITIONS AMONG 80 000 OUTPATIENT AND HOSPITAL CHILDREN*

INCIDENCE (CASES OF EACH DISEASE)	NUMBER OF PREVENTABLE AND CURABLE DISEASES	NUMBER OF ALL OTHER CONDITIONS
Over 200	78 (84%)	18 (10%)
101 to 200	19 (9%)	4 (8%)
26 to 100	47 (22%)	18 (18%)
5 to 25	43 (20%)	46 (35%)
0 to 4	82 (16%)	51 (30%)
Total cases 160,639	214 (100%)	182 (100%)

can be prevented, or cured by specific therapy. The most important diseases, therefore, are those which can be prevented or cured, and the greatest emphasis should be concentrated on recognizing them and on teaching medical students to become familiar with them. Pediatrics can be of the greatest service to the public if in its practice emphasis is placed on the prevention of disease and upon periodic examinations of children for the early detection of disease or disease tendencies, rather than using it as consultative service. For example, it has been found by the investigators of the White House Conference and by others that the health of children who are brought at regular intervals to a physician's office is better than that of those who have medical care only during acute illnesses. Also it is true that for every

TABLE X

THE ONE HUNDRED MOST IMPORTANT DISEASES AND CONDITIONS IN CHILDREN

A Antenatal and Natal Preventable Causes (Responsible for One quarter of the Deaths Among Children)

CONDITION	RELATIVE INCIDENCE*	RELATIVE MORTALITY†
Birth injuries	44x	6
Conditions of early infancy (atelectasis, suffocation, debility, icterus, selemia, etc.)	94x	5
Gonorrheal ophthalmia	83	57
Prematurity	36	1
Stillbirths	99x	95
Syphilis	23	18
Subtotal A (6 conditions)	2%	26%

B Postnatal Preventable Causes (Responsible for One quarter of the Deaths Among Children)

Accidents (incl trauma)	66x	13
Anemia	81	45
Chickenpox	46x	68
Dehydration	93x	71
Dietary deficiencies (pellagra, rickets, scurvy, carious teeth, tetany)		87
Diphtheria	2	7
Dysentery (bacillary)	33x	3
Enuresis	25	74
Feeding regulation	29	75
Intertrigo	4	81
Malaria	56	29
Malnutrition	89	83
Measles	13	15
Nutritional disturbances	35x	4
Pertussis	7	9
Poisoning	17x	64
Rabies	63	58
Scarlet fever	100x	19
Smallpox	51x	60
Tetanus	98	33
Tuberculosis (incl the meningitis)	96	10
Typhoid paratyphoid fever (typhoid, para A, para B, B supestifer)	9	27
Vaginitis	59	100
Subtotal B (23 conditions)	34	—
	30%	27%

C Causes Curable by Specific Therapy (Responsible for One fifth of the Deaths Among Children)

Abscesses	1	44
Acidosis	80x	66
Adenoids	14	65
Allergy (exc urticaria)	12	51
Anemia (sec B)		
Appendicitis	85x	16
Arthritis	37	54
Bacteremia	64	47
Behavior problems	16	67
Bronchitis	11	17
Chorea	38	61
Conjunctivitis (exc gonococcus)	28	69
Constipation	39	70
Convulsions	67	24
-Dehydration (see B)		
Dermatitis	41	72

TABLE X—CONT'D

C Causes Curable by Specific Therapy (Responsible for One-fifth of the Deaths Among Children)

CONDITION	RELATIVE INCIDENCE	RELATIVE MORTALITY†
Diabetes mellitus	90	39
-Deficiency diseases (see B)		
-Diphtheria (see B)		
Dysentery (amebic)	97	73
Empyema	58	38
Epilepsy	43	43
Erysipelas	72	31
Eye abnormalities	26	59
Fracture	61	76
Fungus infections	55	53
Gastritis	69	41
Hemophilia	95	77
Hemorrhagic disease of the newly born	88	78
Hernia	15	49
Hydrocele	70	70
Impetigo	21	80
Intussusception and intestinal obstruction	81	22
Laryngitis	52	40
Lung abscess and bronchiectasis	92	63
-Malaria (see B)		
Mastoiditis	75	35
Meningitis (mge)	68	30
Miliaria	78	84
Neurosis	40	85
Otitis media	3	28
Parasites (intestinal)	45	52
Pediculosis	50	86
Pneumonia	8	2
Prepuce abnormalities	19	87
Purpura	86	88
Pyloric stenosis	79	39
Pyuria	32	62
Retardation (physical)	73	91
Rheumatic fever	47	32
Scabies	30	93
Sinusitis	82	94
Stomatitis	27	48
-Syphilis (see A)		
Tic	74	96
Tonsils hypertrophy of	10	97
Thymus enlargement	84	26
Thyroid abnormality	81	56
Ulcers	77	98
-Tuberculosis (see B)		
Tumors (abdom. brain misc.)	42	34
Urticaria	54	99
Subtotal C (55 conditions)	45%	21%

D Diseases Preventable by Public Health Measures

Influenza	63	11
Mumps	65x	55
Pollomyelitis	49	23
Subtotal D (3 conditions)	1%	3%

TABLE X—CONT'D

E Common Diseases Which at Present Cannot Be Prevented or Cured by Specific Measures

CONDITION	RELATIVE INCIDENCE*	RELATIVE MORTALITY†
Encephalitis	60	36
Heart disease (acquired)	24	12
Heart disease (congenital)	48	8
Hydrocephalus	71	25
Jaundice	53	82
Leucemia (all types)	91	42
Lymph node enlargement	20	50
Malformations	22	14
Nephritis	57	21
Peritonitis	76	40
Retardation (mental) (incl idioey)	18	90
Rhinopharyngitis	5	92
Tonsillitis	6	20
Subtotal E (13 conditions)	17%	10%
Total A + B + C + D + E (100 conditions)	95%	87%
246 remaining diseases and conditions	5%	13%
Total 346 diseases and conditions	100%	100%

*Based upon 150 539 cases of 346 diseases and conditions among 80 000 children in the Harriet Lane Home, Johns Hopkins Hospital 1912 to 1932 figures marked (x) are not representative of the true relative incidence, because patients suffering from these conditions usually were on other services i.e. conditions of early infancy and stillbirths on the obstetrical service accidents and appendicitis on the surgical service, diphtheria, measles and scarlet fever on the contagious service, etc. 1 indicates the most common disease 100 the least. (Arena, J. M. and Harriess R. R. Census of the diagnosis file of the Harriet Lane Home [in press])

†Based upon 240 661 deaths among children under fifteen years of age 1927 U.S.A. Mortality Statistics 1 indicates the highest number of deaths 65 the smallest no figures could be obtained for those conditions marked 66-100

dollar paid by the parents of children who are brought regularly to their physicians' offices, three dollars are paid by those who call for medical aid only during emergencies

SUMMARY

As may be seen in Table X, if proper antenatal, natal and post natal preventive measures are perfectly performed, the twenty-nine diseases in groups A and B can be reduced to a minimum, and the pediatrician or family physician can confine his efforts to the diagnosis and treatment of the fifty-five conditions amenable to specific therapy. In other words, instead of trying to teach students and ourselves to recognize three hundred and forty-six diseases, the prevention of twenty-nine, and the treatment of fifty-five should be stressed. These preventable and curable diseases cause 77 per cent of the deaths in children. The present reduction of general mortality largely has been due to efforts to prevent disease, and future progress probably will consist in improving the medical and hospital care of patients, but in pediatrics, as these figures only too clearly demonstrate, emphasis on both phases must be increased. If a physician is trained to recognize all children, if he will carry out the immunization measures which are

recommended by the White House Conference, and if he will feed children simply and sensibly, the practice of pediatrics will progress, the public will be benefited, and infant mortality decreased. If the doctors, health departments and public will cooperate, this goal can be reached. Much of the present situation is due to the apathy and indifference of the public, and not to any unwillingness of the medical profession. The accusation of Lady Mary Montagu is as unfounded today as it was in 1717. "I am patriot enough to take pains to bring this useful invention (smallpox inoculation) into fashion in England, and I should not fail to write to some of our doctors very particularly about it, if I knew any one of them that I thought had virtue enough to destroy such a considerable branch of their revenue for the good of mankind. But that distemper (smallpox) is too beneficial to them, not to expose to all their resentment, the hardy wight that should undertake to put an end to it. Perhaps, if I live to return, I may, however, have courage to war with them. Upon this occasion, admire the heroism in the heart of—our friend Mary Wortley Montagu."

REFERENCES

- 1 Bass, C. C. South. M. J. 21: 1049, 1928.
- 2 Grulice, C. G. Proc. Congress Med. Educ. Med. Ill. & Hospitals, Chicago Feb. 16-18, 1931: 1-4.
- 3 Osler, W. Acquaintances, Philadelphia, 1904. I. Blakiston & Son & Co., p. 140.
- 4 Stewart, C. A. Am. J. Dis. Child. 43: 803, 1930.
- 5 Chew, S. Lectures on Medical Education or on the Proper Method of Studying Medicine. Philadelphia, 1864. Lindsay & Blakiston, 152 pp.
- 6 Arens, J. M. and Harris, R. R. Census of the Diagnosis File of the Harriet Lane Home (in press).
- 7 From the Trend of Health. American Child Health Association. (Chapter 1: Health Education).
- 8 The causes of death among 1052 children under fifteen years of age admitted for all conditions (except surgery in those over two years of age and infectious diseases) to the Harriet Lane Home (the children's department of the Johns Hopkins Hospital) from July 1, 1930 to June 30, 1931.
- 9 Gengenbach, F. P. J. Pediat. 1: 710, 1932.
- 10 Brooks, B. U. South. M. J. 23: 860, 1930.
- 11 Epstein, I. M. Am. J. Dis. Child. 41: 1363, 1931.
- 12 Quotation from a letter of the Right Honorable Lady Mary Wortley Montagu, London, printed from T. Beckett and P. A. DeHondt on the Strand, 1703, volume 2, pages 62 and 63.

SERUM PROTEINS AND LIPOIDS IN THE ECZEMA OF INFANTS AND CHILDREN

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IT IS now some twenty-eight years since Czeiny¹ introduced the term "exudative diathesis" into medical nomenclature. His purpose was in part to remove the confusion with tuberculosis which the older term "scrofula" (Skrophulose) involved, but mainly to emphasize his conception of the disorder as one based on heredity and constitution in which metabolism, particularly of the fats, was seriously at fault and of which the skin disturbance was but one manifestation. Although at that time the modern conception of allergy had not been defined and elaborated, Czerny called attention to the importance in the clinical picture of idiosyncrasies to various foods, to the frequency of urticaria, and to the occurrence of asthma and allied respiratory disorders as a later event in patients with the exudative diathesis. While today, at least in America, the term is not widely used, it has played an important part in developing the now generally accepted view that what is usually called "infantile eczema" is in reality but one of the evidences of a constitutional anomaly.

In many respects our knowledge of the basic nature of this common and distressing disorder remains defective. An enormous literature has grown up around the subject, which it is impossible to review in this paper (see the recent publications of Moro² and Hill³). That a state of allergy occurs in a large proportion of cases is well established but whether this is the primary or a secondary phenomenon is uncertain. The recent study of Smyth, Bain and Stallings⁴ would appear to indicate that skin allergy, at least, is characteristically a later development, increasing notably from the earlier to the later months of the first year, and that hypersensitiveness of the skin to various nonspecific irritations definitely precedes it.

In the search for clues to the nature of the underlying disturbance rather than with preconceived notions as to what this might be, we have made some analyses of the blood of a sort previously little studied. These included the total protein, the albumin, the globulin, the cholesterol and (in part of the cases) the lipid phosphorus.

Previous studies of the serum proteins and lipoids in the eczema of infants and children are few and present observations in small numbers of cases only. Rubadeau Dumas and Levy,⁸ using the Kjeldahl method, reported a slight hypoproteinemias in 5 infants with active eczema, and normal figures in 3 others after healing. Goldbloom and Gottlieb⁹ reported high cholesterol in 3 of 4 cases of eczema, they used whole blood, not serum, and their absolute figures are not comparable with ours. In other reports found in the literature the patients were either adult, or the age was not stated. The study of Perutz and Klein⁷ on adults may be mentioned, since they found high albumin/globulin ratios and high osmotic pressures in the serum during the stage of repair in eczema while the values were approximately normal during the acute stages.

METHODS

Total protein was determined by the gravimetric method of Barnett, Jones and Cohn.¹⁰ The same method was also used for albumin after separation of this protein fraction with half saturated ammonium sulphate. Globulin was also similarly determined but the figures used in the present report represent determinations by difference (total protein-albumin), since the amounts of globulin in most of the samples were too small for entirely satisfactory accuracy in direct measurement. The method of gravimetric measurement has an important advantage over other methods available for the analysis of small samples of blood, being more accurate in our opinion than micro-Kjeldahl measurements, and quite independent of possible variations in amino acid composition of the proteins, as contrasted with colorimetric methods.

Cholesterol was determined by the method of Myers and Wardell.¹¹ The lipid phosphorus was determined by a combination of the methods slightly modified, of Bloor¹² (preliminary extraction) and Benedict and Thel¹³ (determination of phosphorus).

Colloid osmotic (oncotic) pressure was estimated by the formula of Gornvarts.¹⁴

Osmotic pressure = (albumin \times 55) + (globulin \times 1.4). The accuracy of this formula in correspondence with the actual oncotic pressure of the serum as a whole is perhaps not entirely satisfactory but probably gives a reasonable approximation.

MATERIAL

Fifty infants and children with typical eczema were studied. Total protein was determined in all of these. albumin (and, hence, the derived figures for globulin albumin/globulin ratio osmotic pressure) in 46 of them. For comparison samples of blood were taken from 36 infants and children without eczema present or past and either in good health or brought to the clinic for minor complaints. In one of these the distribution of albumin and globulin was manifestly abnormal (albumin, 1.59 globulin 5.19) and in one the cholesterol (297 mg per cent) was extremely high both these were excluded from the computations of the control figures.

Our serum samples being small cholesterol and lipid phosphorus were determined in the alcohol-ether washings of the protein precipitates.

TABLE I

	TOTAL PROT		ALBUMIN		GLOBULIN		A/G RATIO		ONCOTIC PRESSURE		CHOLESTEROL		LIPOID P	
	GM PER CENT		GM PER CENT		GM PER CENT				MM HG		MG PER CENT		MG PER CENT	
	CNTR	ECZ	CNTR	ECZ	CNTR	ECZ	CNTR	ECZ	CNTR	ECZ	CNTR	ECZ	CNTR	ECZ
No cases	36	50	35*	40	31*	40	33*	46	35*	40	33*	42	21	22
Mean	6.73	6.86	4.72	5.04	2.01	1.83	2.60	3.03	28.44	30.27	163.7	200.3	8.76	8.58
Median	6.70	6.93	4.81	5.03	1.93	1.77	2.62	2.70	28.80	30.55	170.2	200.0	7.76	8.43
Prob error (\pm)	0.50	0.51	0.35	0.45	0.48	0.37	0.56	0.67	1.86	2.37	17.0	31.5	2.05	1.06
Diff means (per cent contr mean)	+2%	+7%	+7%	+9%	-9%	+12%	+12%	+5%	+5%	+22%	+22%	-2%	-2%	-2%
Per cent cases over contr mean	50%	58%	51%	61%	43%	33%	54%	59%	60%	59%	53%	81%	39%	41%

*One case omitted

Cholesterol was determined in 42 of the eczema group, and 34 of the control group. Lipoid phosphorus was determined in 22 of the former, and 21 of the latter.

The age distributions of the two groups were reasonably similar. In the eczema group, 12 (24 per cent) were six months or less, 14 (28 per cent) between six months and a year, 12 (24 per cent) between one and two years, and 11 (22 per cent) two years or older. In one case the age was not stated. In the control group, 9 (25 per cent) were six months or less, 7 (19 per cent) between six months and a year, 6 (17 per cent) between one and two years, and 14 (39 per cent) two years or older. Since the main physiologic changes in proteins and lipids occur during the first six months and the main differences between the age distributions of two groups occurred after the age of six months, we believe that the latter are not of significant proportions for our purposes.

EXPERIMENTAL RESULTS

Total Protein—No significant difference in total protein is detectable between the groups with and without eczema. The former show a slightly higher average figure, and about 8 per cent more of the eczema sera than of the controls were above the normal average. The variability is equal in the two groups.

Serum Albumin—The difference between the two groups is somewhat more striking than is the case with total protein, but not, perhaps sufficient to constitute statistical significance. The eczema average is 7 per cent higher than that of the controls, and 10 per cent of the cases showed figures greater than the control average. The variability in the former was however greater than in the controls. On the whole a tendency to higher serum albumin in eczema is suggested by the data, but it is manifestly inconstant.

Serum Globulin—As might have been expected from the total protein and albumin, the globulin percentages in the eczema group are, on the average, somewhat lower (9 per cent) than in the control group. Sixty-seven per cent of the eczema group showed figures for globulin lower than the control average. The variability is distinctly lower in the eczema than in the control group.

Albumin/Globulin Ratios—The mean of the eczema group is 12 per cent higher than that of the control group, but the variability is quite large. Some extreme deviations of the ratios occurred in the eczema group, in four instances, they were in excess of 4.5 and in one instance, reached the remarkable figure of 7.7.

Osmotic Pressure of the Proteins (Oncotic Pressure)—The tendency to slightly higher total protein and considerably higher albumin fractions in the eczema group indicated that the protein osmotic pressure would be abnormally high in many cases. This was found true, since

TABLE I

	TOTAL PROT GM		ALBUMIN GM		GLOBULIN GM		A/G RATIO		ONCOTIC PRESSURE MM HG		CHOLESTEROL MG		LIPOID P MG	
	CNTR	ECZ	CNTR	ECZ	CNTR	ECZ	CNTR	ECZ	CNTR	ECZ	CNTR	ECZ	CNTR	ECZ
No cases	36	50	35*	46	35*	46	35*	46	35*	46	33*	42	21	22
Mean	6.71	6.86	4.72	5.04	2.01	1.83	2.60	3.03	28.44	30.27	163.7	200.3	876	858
Median	6.70	6.93	4.81	5.03	1.93	1.77	2.62	2.70	28.80	30.55	170.2	200.0	776	843
Prob error (\pm)	0.50	0.51	0.35	0.45	0.48	0.37	0.56	0.67	1.86	2.37	17.6	31.5	2.05	1.06
Diff means (per cent contr mean)		42%		47%		-9%		+12%		+5%		+22%		-2%
Per cent cases over contr mean	50%	58%	51%	61%	43%	13%	54%	59%	60%	59%	55%	81%	39%	41%

*One case omitted

however, not accurately quantitative and was also positive in some of our controls. We are, therefore, unable to draw any direct conclusions from our few precipitin tests.

The hypercholesterolemia occurring in at least half of our cases of eczema—the most constant abnormality noted—as well as the much greater “scatter” of the figures for cholesterol in that group (one of which was as low as 70 mg per cent), while of obscure significance, suggest a marked instability of cholesterol metabolism as a frequent, though not constant, accompaniment of eczema.

CONCLUSIONS

1 In the eczema of infants and children, apparently independent of age or the state or stage of the disease, the composition of the serum protein frequently but not constantly shows deviations from the normal. The commonest changes in the proteins are high albumin, low globulin, and a high albumin/globulin ratio, all of which occur more frequently in patients with eczema than in those without the disease. These changes involve an increase in the calculated oncotic pressure of the serum. It is to be emphasized that the changes when observed are not except in a minority of cases extreme, they are not constant or suggestive of more than a secondary effect of the disease.

2 An inconstant but much more frequent change is hypercholesterolemia. In one half of the cases of eczema the level of serum cholesterol was found to be in excess of 200 mg per 100 cc, and the average of the group as a whole was also slightly over that figure. In a few cases the cholesterol was very low. The results indicate a certain instability in cholesterol metabolism in eczema, the significance of which is not clear but which is probably to be regarded as a secondary or subsidiary manifestation of the general disturbance. No differences in the phospholipids of the serum were detected in the eczema group as compared with the controls.

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REFERENCES

- 1 Czerny A. *Jahrb f Kinderh.* 61 190, 1905
- 2 Moro E. *Eczema Infantum und Dermatitis Seborrhoeica*. Berlin 1932 Julius Springer
- 3 Hill, L. W. *J Pediat.* 2 133 1933
- 4 Smyth F S., Bain K. M., and Stallings, M. *J A M. A.* 97 1291, 1931
- 5 Ribadeau Dumas, M. L., and Levy, M. M. *Bull. et mém. Soc. méd. d. hôp de Paris* 52 51, 1928.
- 6 Goldbloom, A., and Gottlieb R. *Canad. M A J* 17 1383 1927
- 7 Perutz A., and Klein A. E. *Arch. f Derm u. Syph.* 185 532 1932.
- 8 Barnett, C. W., Jones, R. B., and Cohn, R. B. *J Exper Med* 55 683 1932
- 9 Myers V C., and Wardall, E L. *J Biol. Chem.* 36 147, 1918
- 10 Bloor W R. *J Biol. Chem.* 38 33 1918
- 11 Benedict, S. R., and Theis, R. C. *J Biol. Chem.* 61 63 1924.
- 12 Cited in: Peters, J P., and Van Slyke D D. *Quantitative Clinical Chemistry*, Baltimore, 1931, The Williams and Wilkins Co, vol. I, p 650.

INTRACELLULAR FLUID LOSS IN DIARRHEAL DISEASE

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INTRODUCTION

THE process of the dehydration of infants in the course of diarrheal disease may be briefly described. Vomiting and diarrhea produce a loss of gastrointestinal secretions and thereby cause a withdrawal from the blood plasma of the water and materials used in the construction of these secretions. The blood plasma is, however, sustained over a considerable interval, both as regards volume and composition, at the expense of interstitial fluid and the extensive loss of interstitial fluid which is so conspicuously evident in dehydrated patients is thus produced. Eventually the interstitial reservoir is depleted and then, with dangerous rapidity, the volume of the plasma falls and distortions of the electrolyte structure of the plasma develop¹. It is thus apparent that an essential step in the repair of dehydration should consist in refilling the interstitial body fluid compartments. This is usually accomplished by the subcutaneous administration of physiologic salt solution which provides the two quantitatively important electrolytes, sodium and chloride ion. With more finesse, a solution which copies in detail the composition of interstitial fluid may be used².

There remains for consideration the possibility that dehydration produces also a withdrawal of appreciable quantities of intracellular fluid. The implications of such an event must be considered in terms of the electrolyte content of intracellular fluid as compared with that of the extracellular fluids. As may be seen in the diagrams in Fig 1, there are only slight differences in the relative values of the inorganic factors in the composition of blood plasma and of interstitial fluid. These differences are referable, in terms of the Donnan law, to the presence of the nonpermeating protein ions in the plasma. Intracellular fluid, however, presents an electrolyte pattern which differs widely from that of the extracellular fluids. Here, instead of sodium, potassium is the chief factor in the total fixed base value and phosphate almost replaces chloride. The mechanism which permits these large differences in the values for the individual electrolytes in the two adjacent fluids has not been discovered. It is evident from their

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chemical anatomy as described by the diagrams that intracellular fluid cannot be used, as is interstitial fluid, in support of the blood plasma and also that the materials therapeutically supplied for replacement of interstitial fluid will not repair a loss of intracellular fluid

Does the withdrawal of interstitial fluid which dehydration produces proceed without disturbance of intracellular fluid volume? There is evidence which indicates an accompanying loss of intracellular fluid. It has been found that when interstitial fluid is removed by

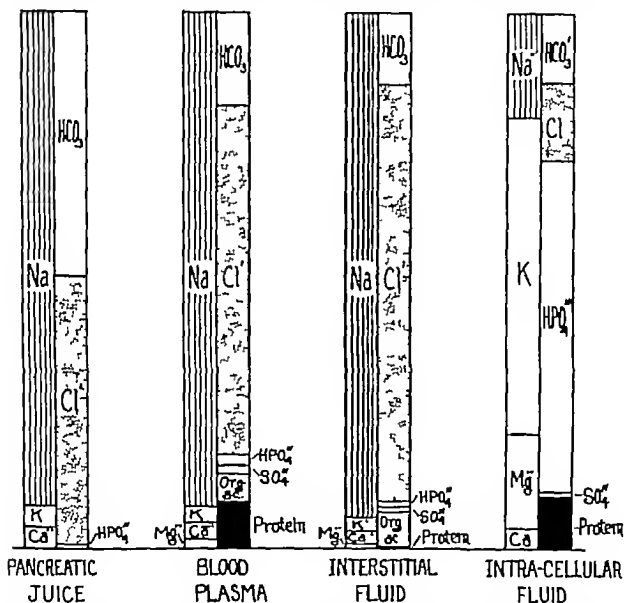


FIG. 1.—Showing the relative values for the concentrations of electrolytes in body fluids. The values for the cations or potential base are superimposed in the left hand columns and those for the acid radicals in the right hand columns. The data representing interstitial fluid are from cerebrospinal fluid and those for intracellular fluid are from muscle tissue.

diuretic agents there occurs also a much smaller but appreciable withdrawal of intracellular fluid.^{1, 4} Apparently, a reduction of the volume of interstitial fluid in the body does to some extent interfere with the maintenance of a normal volume in the adjacent intracellular compartment.

In the studies just cited the information regarding the source of the fluid removed from the body was obtained by measuring the excretion

of sodium and of potassium in the urine. If the fairly satisfactorily established proposition that a loss of electrolyte from the body is accompanied by a corresponding amount of water be accepted, measurements of a loss of sodium and of potassium can, as the data in Fig 1 indicate, be used to calculate respectively a withdrawal of extracellular and of intracellular water. This premise is used in an investigation of body fluid losses by infants in the advanced and severe stage of diarrheal disease, the results of which are presented in this paper. The chief item of attempt was to learn whether or not there is a considerable loss of intracellular fluid in addition to the large loss of interstitial fluid.

PLAN OF STUDY

Two infants were studied over a period of twenty-four hours immediately following their entrance to the hospital. Both were suffering severely from diarrheal disease with vomiting and were extensively dehydrated. So far as could be determined, no food had been retained for several days. They were given no food during the twenty-four hour period but did receive salt solution subcutaneously and glucose solution intravenously. The substances measured in the urine and stools may therefore be taken as describing losses from the body. Sodium and chloride from the administered salt solution can probably correctly be included in this statement since the quantities supplied were doubtless less than the deficits which dehydration had produced. With the hope of obtaining a urine specimen before beginning treatment, the fluids were not administered until after the first eight hours. Catheterization then, however, failed to produce a specimen. The infants were thus evidently anuric, and the urine secreted during the subsequent sixteen hours may be regarded as a response to the fluids given. The infants were comfortably immobilized on the metabolism bed and a collection of urine and of stools over the twenty-four hour period was obtained. In order to insure a complete urine specimen, the infants were catheterized at the end of the period. One of the infants (A) vomited a few cc of fluid. With this exception vomiting, which had been frequent before entering the hospital, was absent during the period of study. Blood samples were taken at the beginning and at the end of the twenty-four-hour interval.

Measurements of total fixed base, sodium, potassium, phosphorus and nitrogen were obtained from both urine and stools. The concentrations of total fixed base, chloride, and carbon dioxide content were determined in the serum of the blood samples, collected and separated under oil.

The following methods of analysis were used: total base by the method of Fiske, sodium by uranyl zinc acetate precipitation as described by Butler and Tuthill⁶, potassium by Fiske's modified cobaltinitrite method in which potassium is reprecipitated as potassium acid tartrate⁷, phosphorus by the method of Fiske and

Subbarow⁸, chloride by Fiske and Lin's method of wet ashing with nitric acid and potassium permanganate and Volhard titration⁹, carbon dioxide content of the serum according to Van Slyke and Sendroy¹⁰ and nitrogen by macro-Kjeldahl.

RESULTS AND DISCUSSION

If the loss of body fluid in diarrheal disease caused by failure of reabsorption of gastrointestinal secretions is limited to extracellular fluids and if the quantity of intracellular fluid presenting for excretion is determined only by the extent to which body protoplasm is destroyed as a result of the factor of fasting which the situation contains, the composition of the fixed base excretion in urine and stools can be postulated readily by reference to the diagrams in Fig 1. In other words nearly all of the fixed base in the stools should be sodium and, owing to the sodium deficit thus produced within the body, no sodium should be permitted to enter the urine. The fixed base in the urine should consist chiefly of potassium, the amount of which should correspond to the extent of the destruction of body protoplasm as indicated by the nitrogen excretion.

The measurements actually obtained from the two infants (Tables I and II) extensively disobey these expectations. In both instances the quantity of potassium in the stools is, in relation to sodium, very much larger than would be expected on the basis of the relatively small value for potassium in gastrointestinal secretions and in the extracellular fluids (Fig 1). The urines both contain appreciable quantities of sodium which however, are small fractions of the amounts of sodium supplied by the administered salt solution. The expected considerable excretion of potassium is found. When, however the loss of intracellular fluid calculated from the urine potassium is compared with the loss of fluid as estimated from urine nitrogen it is found to be much larger. These calculated values are given in the third section of the tables*. It thus seems that potassium and a corresponding quantity of intracellular water are excreted in the urine to a much greater extent than can be accounted for by the destruction of body protoplasm as measured by the nitrogen excretion†. The

The formulas used in calculating the extra and intracellular fluid losses were those of Peters and Van Slyke¹¹

$$\frac{Na - 0.45 K}{148} = \text{liters of extracellular water lost.}$$

$$\frac{K - 0.017 Na}{112} = \text{liters of intracellular water lost.}$$

in which Na and K represent milligram equivalents of base found. As regards the 0.0 value for extracellular water in urine which was found for both infants, it may be noted that the factor 0.425 K in the first equation produced values for Na from intracellular water of 2.10 m-eq. for infant A and 1.23 m-eq. for infant B, which very closely cancel the found values for Na given in the table, 1.87 m-eq. and 1.25 m-eq. respectively.

The intracellular fluid loss corresponding to destruction of protoplasm was calculated from the formula

$$\text{Nitrogen (gm.)} \times 9.6 \times 76 = \text{c.c. water}$$

†Any nitrogen lost through the skin could not account for the excess of excretion of potassium over nitrogen in the urine and stools as available data indicate that the ratio of nitrogen to potassium in sweat is less than that obtaining in protoplasm.

TABLE I

INFANT A AGED THREE MONTHS WEIGHT 10 POUNDS

Diarrhea and Vomiting Four Days Evident Dehydration Fluids Given 10% Glucose Solution, Intra v, 150 cc 0.9% Salt Solution, Sub c, 200 cc. (= 31 mmol NaCl)

Data from Blood Serum

	FIXED BASE M EQ PER L	CO ₂ CONTENT M EQ PER L	CHLORIDE M EQ PER L
At entrance	126	21.2	78
After 24 hours	142	19.6	90

Data from Urine and Stools

	VOLUME CC	FIXED BASE M EQ PER L		Na		K		HPO ₄ *		N MG
		M EQ	M EQ PER L	M EQ	M EQ PER L	M EQ	M EQ PER L	M EQ	M EQ PER L	
Urine	191	1.07	10.9	4.93	27.2	5.60	31.0			929
Stools	17	2.97	66.0	1.78	39.5	0.99	22.0			196
Total	208	4.94	-	6.71	-	6.59	-			1125

*In terms of base equivalence at reaction of body fluids. *Pr* 7.4

Calculated Losses of Body Water

	EXTRACELLULAR		INTRACELLULAR		
	FROM Na	FROM K	FROM N	"WITHDRAWN"*	
	C.C.	C.C.	C.C.	C.C.	
Urine	0.0	43.7	20.8	22.9	
Stool	14.9	15.4	4.4	11.0	
Total	14.9	59.4	25.2	34.2	

*Water from K-Water from N

Sodium retention, 80.0% Na supplied in salt solution
Sodium loss in urine, 6.3% Na supplied in salt solution
Sodium loss in stools, 9.6% Na supplied in salt solution

TABLE II

INFANT B. AGED THREE MONTHS. WEIGHT 6 POUNDS.

Diarrhea and Vomiting Six Days. Extreme Dehydration. Fluids Given 10% Glucose Solution, Intrm v, 105 c.c. 0.9% Salt Solution, Sub-c, 250 c.c. (= 30 mmol NaCl)

Data from Blood Serum

	FIXED BASE M EQ PER L	CO CONTENT M EQ PER L	CHLORIDE M EQ PER L
At entrance	116	-	72
After 24 hours	146	13.6	100

Data from Urine and Stools

VOLUME C.C.	FIXED BASE		Na		K		HPO		N MG
	M EQ PER L	M EQ PER L	M EQ	M EQ PER L	M EQ	M EQ PER L	M EQ	M EQ PER L	
Urine	73	50	1.25	17.1	2.80	39.6	2.94	40.4	562
Stools	102	150	13.00	67.7	9.11	47.5	4.37	22.8	614
Total	265	-	14.25	-	12.00	-	7.31	-	1176

In terms of base equivalence at reaction of body fluids Pn 7.4

Calculated Losses of Body Water

	EXTRACELLULAR		INTRACELLULAR	
	FROM Na C.C.	FROM K C.C.	FROM N C.C.	WITHDRAWN % C.C.
Urine	0	25.6	12.6	18.0
Stool	61.7	79.3	13.8	65.5
Total	61.8	105.0	26.4	78.6

Water from h-Water from N

Sodium retention 64.0% Na supplied in salt solution
 Sodium loss in urine 3.2% Na supplied in salt solution
 Sodium loss in stools, 33.0% Na supplied in salt solution

simplest explanation of this finding is that, in addition to the release of water from destroyed protoplasm, there occurs a withdrawal of water from tissue cells. The extent of this withdrawal of intracellular water is measured by subtracting the value for released water, calculated from the nitrogen measurement, from the total excretion of intracellular water calculated from the potassium excretion. In the stools the value for "withdrawn" water thus obtained constitutes much the greater part of the excretion of intracellular water, and is approximately as large a quantity as the extracellular water loss calculated from the sodium content of the stools. The total value for "withdrawn" intracellular water in the urine and stools taken together is, in both experiments, actually larger than the total excretion of extracellular water.

The measurements obtained from the initial blood serum samples show extensive changes from their normal values for the three quantitatively important structural factors and demonstrate that the process of dehydration has passed the point beyond which the plasma cannot be accurately sustained by water and materials from the interstitial reservoir.

The major finding from this study of two infants in an advanced stage of dehydration is the evidence just presented demonstrating that, in addition to the loss of interstitial fluid, which we are accustomed to regard as the essential event, there is operative also a process of withdrawal of intracellular fluid producing a water loss which is quantitatively even larger than the loss of interstitial water.

The data obtained from these infants do not explain the process of withdrawal of intracellular fluid. An especially puzzling feature is its removal to a large extent in the stools, which under the conditions of this study, are assumed to be composed of gastrointestinal secretions in which the concentration of potassium has approximately the same small value found in the blood plasma, 5.0 m-eq per liter. In the stools from these infants, the concentration of potassium was for A, 39.5 m-eq per liter and for B, 47.5 m-eq per liter. The disability of renal function, which is a consequence of severe dehydration, probably somewhat raises the level of potassium in the plasma. Direct information on this point is unfortunately lacking. It has been found, however, that in advanced renal disease the concentration of potassium is rarely more than double the normal value. The subjects of this study received glucose solution which presumably enabled the kidneys to operate fairly accurately as indicated by the secretion of a sizable volume of rather dilute urine. It is, therefore, altogether improbable that potassium accumulated in the extracellular fluids to an extent sufficient to explain directly the high values found in the stools.

There is some temptation to suggest a substitution of potassium for sodium by the secretory mechanisms in supporting the required osmolar value of the intestinal fluids. That the total concentration of

electrolytes was sustained at approximately the body fluid level is shown by the rough agreement of the total fixed base concentration in the stools with the values for fixed base found in the plasma. It is, however, physiologically unlikely that unusual substances could be employed in the construction of secretions and, since these infants received sodium chloride solution, there is little basis for supposing a purposeful or compulsory substitution of potassium and phosphate for the regularly used materials, sodium and chloride.

Another conjecture contains, to our minds, some degree of probability. This consists in postulating a much more rapid absorption of sodium than of potassium from the bowel with the result that the potassium content of the stools represents an accumulation derived from the small quantities present in normally constructed secretions. In support of this surmise an observation made by one of us may be cited.¹² In the case of a normal subject when the food contains several times as much sodium as potassium and, moreover encounters during digestion secretions which contain twenty five times as much sodium as potassium, more potassium than sodium is found in the stools. Assuming no reabsorption of potassium, the concentrations of potassium found in the stools of these two infants with diarrheal disease describe an approximately tenfold concentration of gastrointestinal fluids containing, when secreted, the normal value for potassium, 50 m eq per liter. Interestingly it may also be seen in the tables that the concentration of phosphate in the stools is closely ten times the value found in normal blood plasma 2.5 m-eq per liter. Since under normal circumstances there is very little reabsorption of phosphate although potassium is extensively returned to the body fluids, this parallel relationship of the concentrations of potassium and phosphate in the stools of these infants to the normal blood plasma values suggests that diarrheal disease interferes more or less completely with the reabsorption of potassium. In the case of the infant B, whose stool volume was very large 192 cc, a total secretion of nearly 2000 cc of intestinal fluids would be required to account for the tenfold concentration of potassium found. This is a large figure for the secretions but is not of an impossible order of magnitude. The twenty four hour volume of gastrointestinal secretions for a normal adult is 8-10 liters and the surmise is permissible that the volume of the secretions may be much increased in diarrheal disease. Also, a slight increase in the potassium concentration in the plasma above the normal value which is a not improbable event in severe dehydration would greatly reduce the calculated volume of secretions. For instance if the plasma potassium in the infant B be taken as 7.5 m eq per liter instead of the normal value 5.0 m eq per liter, the volume of secretions required to produce the concentration of potassium found in the stools would be 1200 cc instead of 2000 cc. This explanation of the large excretion of potassium in the stools if it could be estab-

lished, would describe a process of withdrawal of intracellular fluid operative whenever abnormal circumstances produce a partial interference with the reabsorption of gastrointestinal secretions

The presence of an intracellular fluid loss complicates our conception of the process of dehydration and disturbs our confidence in the therapeutic adequacy of parenteral treatment. Since repair solutions must be placed in the vascular or in the interstitial compartment, they cannot contain with safety the intracellular materials, such as potassium and phosphate, at concentrations above the small values prescribed for them in extracellular fluids. The solution devised by Hartmann contains potassium appropriately to this extent. It is evident, however, that such solutions cannot provide an adequate replenishment of intracellular materials. Parenteral therapy has a large, often dramatic, effectiveness. It must be admitted, however, that it is not always successful and it may be hoped that recognition of an additional pathologic process in the situation will eventually produce supplementary measures which will provide a more complete control of the severe stage of diarrheal disease.

SUMMARY

Estimations of the extent and source of losses of body fluid by infants in an advanced stage of diarrheal disease were obtained from measurements of the excretion of sodium, potassium and nitrogen in the urine and stools.

It was found that intracellular fluid is excreted in both urine and stools to an extent much greater than can be accounted for by release of water due to destruction of protoplasm. The additional water is regarded as withdrawn from tissue cells. The total quantity of withdrawn intracellular water was found to be larger than the loss of interstitial water.

According to the findings in this study a loss of intracellular fluid, in addition to a loss of extracellular fluid, must be recognized in the process of dehydration produced by diarrheal disease.

REFERENCES

- 1 Gamble, J. L. *New Eng J M* 201 909, 1929
- 2 Hartmann, A. F., and Elman, R. *J Exp Med* 50 387, 1929
- 3 Gamble, J. L., Blackfan, K. D., and Hamilton, B. *J Clin Invest* 1 359, 1925
- 4 Blumgart, H. L., Gilligan, D. R., Levy, R. C., Brown, M., and Volk, M. C. In press
- 5 Fiske, C. H. *J Biol Chem* 51 55, 1922
- 6 Butler, A. M., and Tutthill, E. *J Biol Chem* 93 171, 1931
- 7 Fiske, C. H. Unpublished method
- 8 Fiske, C. H., and Subbarow, Y. *J Biol Chem* 66 375, 1925
- 9 Fiske, C. H., and Lin, K. H. Unpublished method
- 10 Van Slyke, D. D., and Sendroy, J., Jr. *J Biol Chem* 73 127, 1927
- 11 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry—Interpretations*, Baltimore, 1931, Williams and Wilkins, p. 782
- 12 MacKay, E. M., Butler, A. M., and Van Slyke, D. D. Unpublished data

OBSERVATIONS ON THE EFFECT OF AGING ON THE POTENCY OF SPRAY DRIED ANTISCORBUTIC MATERIAL

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ATTEMPTS to protect the vitamin C content of various fruits and vegetables and to obtain it in a concentrated and preserved form have been made rather successfully from the standpoint of retaining a high degree of the potency of the original material by various workers (Chick, Hume, and Skelton,¹ Givens and Cohen,² Givens and McClugage,³ Harden and Zilva,⁴ Harden Zilva and Still,⁵ Givens and McClugage,⁶ and Harden and Robison⁷)

Givens and McClugage⁶ in their experimental study of spray-dried orange juice found that it had retained practically all of its potency three and a half months after manufacture. They concluded their article with the following sentence: "It is suggested that the dried orange juice will serve as a convenient antiscorbutic for use in infant feeding, on polar expeditions, in the navy, and for soldiers during war."

This material, however, later on was found to be, in practice, very hygroscopic.

Goss⁸ in 1925, made a definite statement bringing out this point in his report on orange juice which had been dried by the spraying process two years previously, and which had been found to be still sufficiently potent to cure guinea pigs from scurvy in a dose no greater than that required for fresh orange juice.

Harden and Robison⁷ also referred to the hygroscopic qualities of the concentrated orange juice.

This hygroscopic characteristic of orange juice concentrated alone or with cane sugar, represents a severe handicap in the use of dried orange juice as a practical antiscorbutic.

Bassett-Smith⁹ in 1920, without particularly commenting on this point, seemingly overcame this difficulty by mixing concentrated lemon juice with lactose and gum tragacanth, putting the material in lozenge form. He found that the antiscorbutic potency of this preparation had been retained at the end of twelve months.

The Laboratory Products Company manufacturers of S.M.A., being interested at my behest in making S.M.A. Powder antiscorbutic, finally produced a spray-dried orange juice-lactose combination which was

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but slightly hygroscopic This material was tested in a preventive and in a curative manner on guinea pigs, both at the time of manufacture and thereafter at intervals of one to seventeen months Material from one of the lots of orange juice dried in this manner was fed to a scorbutic infant fifteen months after its manufacture

Beginning with 1924, practical experience with the incorporation of the antiscorbutic vitamin in a powdered milk was obtained when, at my suggestion, in the manufacture of Protein S M A 20 c c of lemon juice per liter of milk were added in the hope of making this mixture antiscorbutic Protein S M A is a powdered acid protein milk similar to lactic acid and casein milks, and has a P_H of 4.6 This acidity was obtained by adding lemon juice and also lactic acid produced by controlled bacterial fermentation of the milk

In order to be quite certain that a powdered milk to which the antiscorbutic vitamin has been added is in reality antiscorbutic, it is necessary to make observations on its antiscorbutic properties weeks, months and preferably years after its manufacture Since 1924 six patients with infantile scurvy at the Babies and Childrens Hospital have been fed this material from five to twenty-three months after manufacture The data obtained on these patients and those on the one human infant and the guinea pigs fed the powdered orange juice described above form the basis of this communication

FRESH ORANGE JUICE, SPRAY DRIED AS A CONSTITUENT OF A LACTOSE ORANGE JUICE MIXTURE

In the fall of 1930 two different lots of fresh orange juice were powdered by the spray drying process That powdered in September has been called Lot No. 1 and that powdered in October Lot No. 2 Lot No. 1 was tested for vitamin C potency both by the preventive and by the curative methods, whereas for Lot No. 2 the curative method only was employed

The powdered orange juice was mixed with water in a manner to make the solution equivalent in content of solids to the fresh orange juice from which it was made For each test of powdered orange juice, a control group of guinea pigs was fed an identical amount of fresh orange juice The diet given both groups of animals was one that has resulted consistently, during a most extensive experience covering many years, in the production of a scurvy in guinea pigs that is fatal at the end of three to five weeks after its institution Both the fresh orange juice and the powdered orange juice solutions were fed daily to the animals with medicine droppers The curves on the informative charts (Figs. 1, 2 and 3) represent the average weights of the three guinea pigs used in each group

Lot No. 1 was packed after drying into small tin cans, the air content of which was not replaced by nitrogen Lot No. 2 was placed in

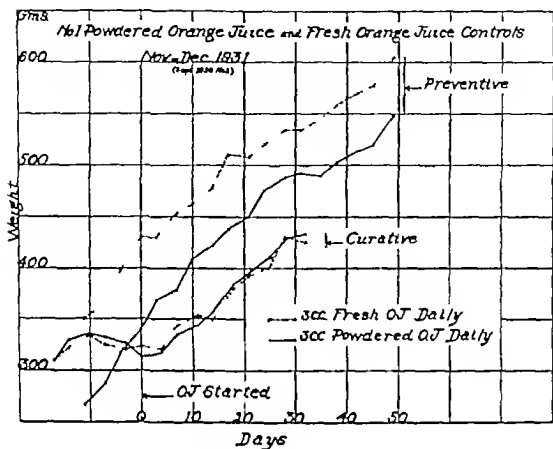


Fig 1—Guinea pig chart. (O J = orange juice)

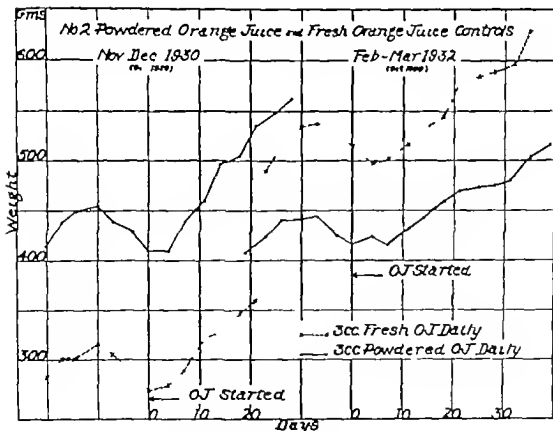


Fig 2—Guinea pig chart.

paper bags which were closed with adhesive tape and placed together in a large ten-gallon milk can, the cover of which was tightly closed. It remained in this environment until July, 1931, when it was repacked under nitrogen in small tin cans.

Fig 1 shows that powdered orange juice Lot No 1 was as effective as fresh orange juice in preventing and in curing scurvy fifteen months after its manufacture. Inasmuch as the fresh orange juice used in feeding the controls was from a different lot of oranges than that used at the time of drying, this result does not prove that Lot No 1 lost none of its antiscorbutic value. However, we feel justified in assuming that whatever loss occurred was small, and is of no practical significance.

Fig 2 shows that Lot No 2 also retained sufficient antiscorbutic potency to cure the guinea pigs of their scurvy. In the first experiment, made when Lot No 2 was one to two months old, the powdered orange juice was as effective as, if not even slightly more so than the lot of fresh orange juice used, judging from the angle of the weight curves. In the second experiment, made when Lot No 2 was fifteen to sixteen months old, the weight curve of the guinea pigs fed the powdered orange juice was not quite so good as that obtained when Lot No 2 was fed at the age of one to two months. This might be considered an indication of a slight reduction in potency. However, that this conclusion is not necessarily correct is shown by Fig 3, which demonstrates that the curve of the guinea pigs fed fresh orange juice, at the time when Lot No 2 at the age of fifteen to sixteen months was being fed, is practically identical with the curve produced by the latter group of guinea pigs and nearly equally different from the curve produced by the scorbutic guinea pigs while being fed Lot No 2 when it was one to two months old. Environmental conditions affecting the animals, probably better than any other factors, can be assumed to have been responsible for this interesting finding.

This interpretation is given apparent corroboration by the rapid cure produced by feeding at practically the same time—namely, during January to March—Lot No 2 to a patient with very severe infantile scurvy, in doses equivalent to a total of 45 cc of fresh orange juice per day (Fig 4).

This patient, R K (No 5580), was one year old when the diagnosis of a very severe infantile scurvy was made. He showed the most severe form of scorbutic rosary seen by us (Fig 5). His gums were pathognomonic and the position of his lower extremities was characteristic. He had been suffering from a purulent otitis media for some time, and a double mastoidectomy had very recently been performed. Drainage was not ceasing and the temperature was not dropping as had been expected after operation. The data presented by Fig 4 show the marked curative effectiveness of powdered orange juice Lot No 2.

the administration of which represented the only change instituted in the care of this patient Fig 6, presenting a photograph taken twenty-three days after treatment, convincingly shows the improvement in nutrition and in the use of his legs Fig 7 gives a photographic reproduction of the roentgenograms of the femurs of this patient, taken just before treatment was begun It presents the well-known changes so characteristic of scurvy Figs 8, 9, and 10 (seventeen, twenty-one, and thirty-nine days after therapy) beautifully demonstrate both the

Fig 5



Fig 6

Figs 5 and 6—R. K. No 5580

extensiveness of the subperiosteal hemorrhages and the therapeutic effectiveness of Lot No 2 It will be noticed in Fig 10 (thirty-ninth day) that the organized subperiosteal hemorrhages had been reduced in size on the inner sides of the femurs and had disappeared entirely on the outer

At this time the supply of Lot No 2 available for use for this infant was exhausted, and therefore 45 c c of fresh orange juice were administered Fig 11 presents the photograph taken at the end of seventeen days of fresh orange juice administration, and Fig 12 that taken on the thirty-eighth day Figs 11 and 12 correspond in time interval after



Figs. 7 9 11

Figs. 8, 10 12

Figs. 7 12.—R. K. No. 5580

the beginning of fresh orange juice therapy with Figs 8 and 10 for the time interval following the giving of Lot No 2 of powdered orange juice

FRESH LEMON JUICE, SPRAY DRIED AS A CONSTITUENT OF PROTEIN S M A

From 1926 to 1932 six patients with infantile scurvy were fed Protein S M A at the Babies and Childrens Hospital as the only food and as the only source of the antiscorbutic vitamin. Figs 13 to 18 present informative charts giving diagnostic, therapeutic, symptomatic and prognostic data in detail. The amount of the lemon juice consumed as a part of the Protein S M A is shown at the lower left hand corner of each chart.

All of the infants with teeth (Figs 13, 17, and 18) showed characteristically swollen, spongy, bluish red gums (see as example Fig 19, patient R S, No 3911 [chart Fig 17]). The others, of course, having no teeth, were negative in this respect.

In each of the six infants a rosary of the bayonet type was present (see as examples Fig 20, patient G P, No 170 [chart Fig 13] and Fig 21, patient R B, No 3774 [chart Fig 16]). That these rosaries were scorbutic and not rachitic in nature can be accepted without question for five of the patients (G P No 170, A S No 774, A Z No 2094, R B No 3774, and R S No 3911) for the following reasons (Table I)

(1) These patients were fed S M A for many months before the treatment of scurvy was begun. This food in our experience has never failed to cure even the severest form of the regular low phosphorus or low calcium types of infantile rickets.

(2) The blood serum calcium and the inorganic phosphorus findings were essentially normal and certainly not characteristic of a rickets which would produce so decided a rosary.

(3) Weekly roentgenograms, both at the time when antiscorbutic treatment was begun and during the period of this treatment, showed no evidence of rickets.

(4) The rosaries disappeared in each instance upon the administration of the antiscorbutic therapy instituted and without the additional use of the antirachitic factor beyond that already being administered previous to and during the development of the scurvy. (See Fig 22, patient R B, No 3774 [chart Fig 16], showing the effect of seventy days of antiscorbutic therapy begun when Fig 21 was taken.)

All of the infants showed somewhere in the osseous system, as studied by x-ray examination, changes that are characteristic of scurvy. The location of these lesions was not uniform in all cases. However, the lower ends of the femurs predominated as the region showing the most clear-cut changes. In none of the children were subperiosteal hemorrhages found to the extent shown in patient R K, No 5580.

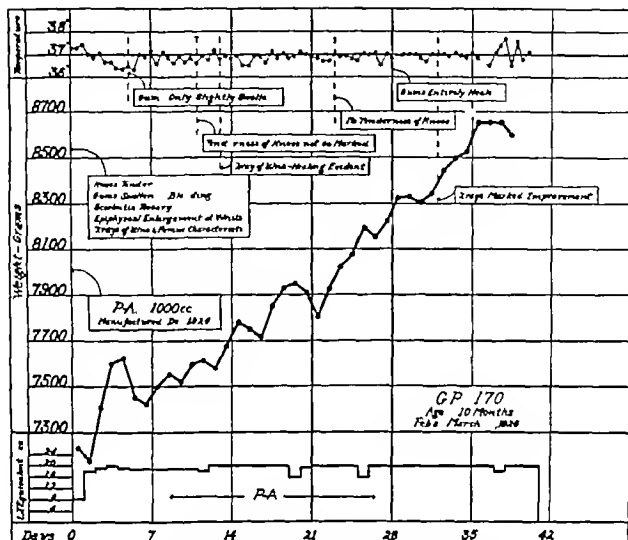


FIG. 13—G P No 170 (P A = Protein B. M. A.)

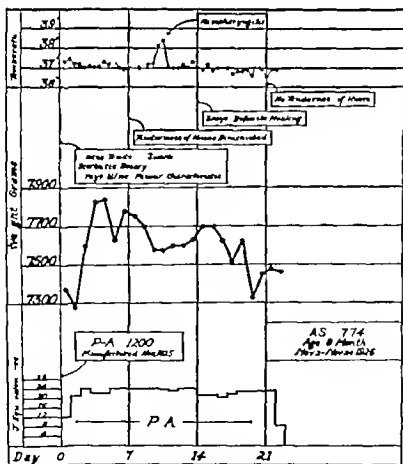


FIG. 14—A. B. No. 774

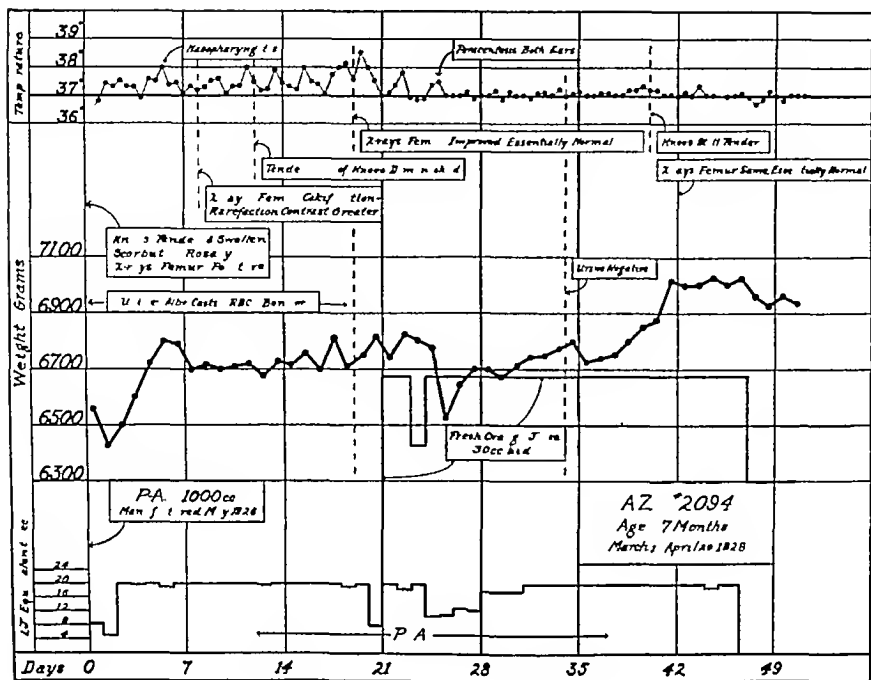


Fig 15—A. Z. No 2094

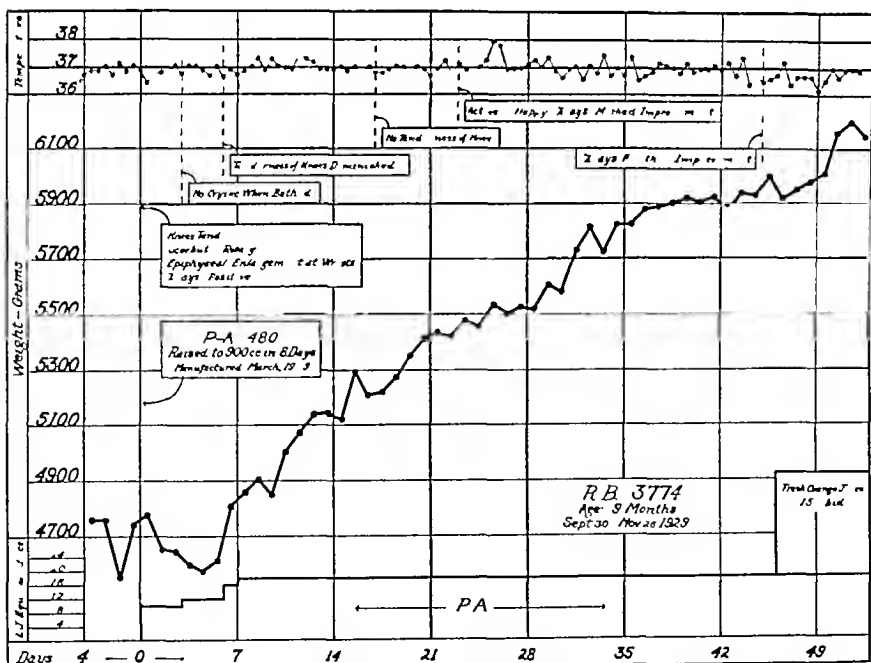


Fig 16—R. B. No 3774

TABLE I

CASE	PREVIOUS DIET	ANTRACHITIS RECEIVED BEFORE ADMISSION	BLOOD SERUM			HOSPITAL	RAY SIGNS OF RICKETS PRESENT	ROSARY PRESENT
			DATE	CA	P			
R. K 5580 Age 1 year Wt 6420 gm	Koller's soup	Yes (OX ceiling lamp Ward 5 West)	1/19/32 1/25 2/3 2/10 2/22 3/14	100 100 56 52 98 109	38 40 56 52 46 60	11/27/31 to 8/20/32	No	Yes Marked scorbutic rosary (bayonet form)
D S 3970 Age 1 year Wt 9375 gm	Milk with Mollin's food	No (information doubtful)	1/5/30 1/10	101 104	44 51	1/3/30 to 3/5/30	No	Yes Moderate scorbutic rosary (bayonet form)
R. S 3911 Age 11 months Wt. 9260 gm	SMA	Yes (SMA)	2/24/30	110	53	12/10/29 to 3/2/30	No	Yes Moderate scorbutic rosary (bayonet form)
R B 3774 Age 9 months Wt 4750 gm	SMA	Yes (SMA)	9/30/29 11/25	110 112	49 60	9/30/29 to 12/13/29	No	Yes Marked scorbutic rosary (bayonet form)
A Z 2094 Age 7 months Wt 6560 gm	SMA	Yes (SMA)	-----	-----	---	3/1/28 to 4/20/28	No	Yes Moderate scorbutic rosary (bayonet form)
A S 774 Age 8 months Wt. 7375 gm	SMA	Yes (SMA)	11/3/26	103	44	11/2/26 to 11/24/26	No	Yes Moderate scorbutic rosary (bayonet form)
G P 170 Age 10 months Wt 7250 gm	SMA	Yes (SMA)	2/18/26	97	50	2/9/26 to 4/22/26	No	Yes Moderate scorbutic rosary (bayonet form)

(Figs 8, 9, and 10), in whom the tendency to hemorrhage evidently existed to a very marked degree

A conclusive proof of the scorbutic nature of the pathologic condition of the bone observed is the fact that all of the lesions improved and the bone sooner or later returned to normal solely upon the administration of the antiscorbutic vitamin in the form of Protein S.M.A (see as examples Figs 23, 24, and 25, patient A Z, No 2094 [chart Fig 15], and Figs 26, 27, 28, and 29, patient D S, No 3970 [chart Fig 18])

It is relatively easy to recognize in the roentgenograms early improvement of the scorbutic changes in a bone but it is at times diffi



Fig. 19—H. S. No. 3911 (chart Fig 17)



Fig. 20—G. P. No. 170 (chart Fig 13)

cult to know when the bone, after the institution of antiscorbutic therapy has reached a complete restitution to normal McLean and McIntosh¹⁰ called attention to this fact in their interesting contribution on 'Healing in Infantile Scurvy as Shown by X Ray'

The roentgenograms of patient A Z show the femurs, first at the beginning of Protein S.M.A feeding (Fig 23 taken March 1, 1928) second seven days later (Fig 24 taken March 8) at which time an increase in the contrast between the excessively calcified line and its adjoining zone of rarefaction had been produced by the treatment, and, third at the time of the disappearance of the rarefied band

(Fig 25, taken March 19, 1928) with an accompanying improvement in the bone structure, eighteen days after the feeding of Protein S M A and three days before the addition of fresh orange juice

McLean and McIntosh¹⁰ also have called attention to this temporary effect of antiscorbutic treatment in augmenting the contrast between the zone of preparatory calcification and the adjoining band of rarefaction (See Fig 24) This contrast between the band of rarefaction and the excessively calcified zone of preliminary calcification is particularly clearly seen in Fig 26, taken Jan 4, 1930 (patient D S, No 3970 [chart Fig 18]) Two weeks later the band of rarefaction (Fraenkel's Trummerfeldzone) has practically disappeared, with an increased filling out and calcification at the lower

Fig 21

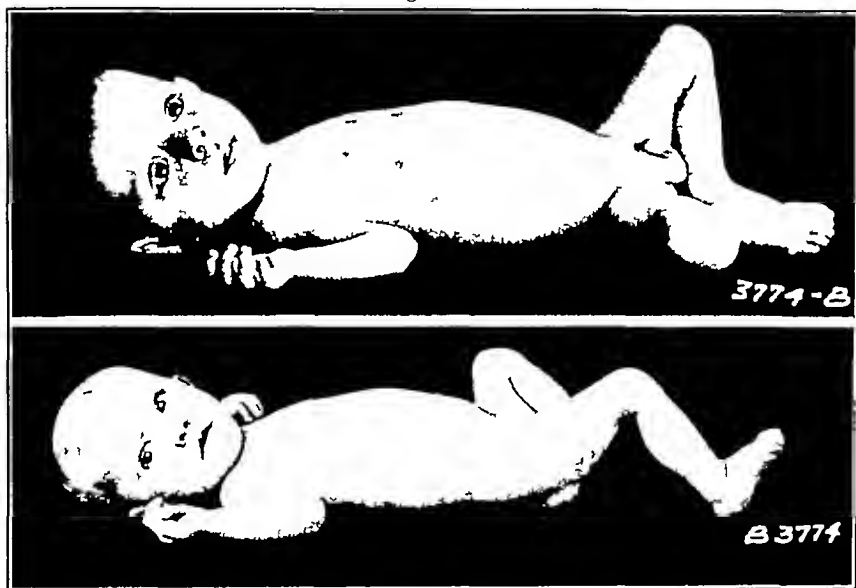


Fig 22

Figs 21 and 22—R. B No 3774 (chart Fig 16)

end of the bone, which on the left side extends slightly underneath the periosteum where probably a hemorrhage had occurred (Fig 27, taken Jan 18, 1930) Ten days later (Fig 28, taken Jan 28) a further decided improvement in the direction of calcification and in contour formation has been made

This very evident improvement in the scorbutic bones of patient D S, No 3970, while coinciding with the disappearance of other symptoms, for instance the swollen gums, was not accompanied by the production of a satisfactory weight curve nor by a normal temperature curve After the taking of the roentgenogram shown in Fig 28 (Jan 28, 1930), 5 gm of brewer's yeast powder were added to the diet three times daily, without any effect on the weight curve,

for this did not rise above its previous level until fourteen days after the administration of the brewer's yeast, at which time, paradoxically, the temperature curve as a result of intercurrent infections became even more abnormal

A very similar experience regarding the delayed return of the weight curve to a normal form, in the face of roentgenographic healing of the scorbutic bones, occurred a few weeks earlier with patient R. S., No. 3911 (chart Fig. 17) to whose Protein S.M.A. brewer's yeast was added on the thirtieth day after the beginning of therapy, in the hope of improving the weight curve. The failure to obtain a positive result at the end of a week was responsible for the addition of 5 c.c. of fresh orange juice daily to the Protein S.M.A. and pow

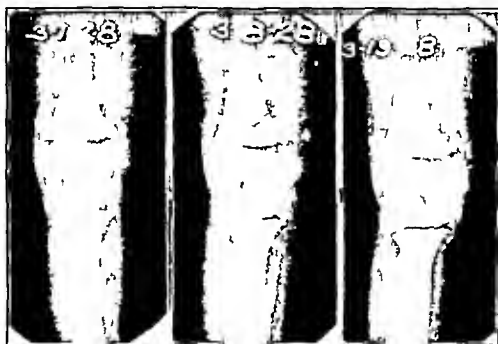


Fig. 23.

Fig. 24

Fig. 25

Figs. 23-25—A. Z. No. 2094 (chart Fig. 19). Fig. 23, taken March 1, 1928. Fig. 24, taken March 8, 1928. Fig. 25 taken March 19, 1928.

dered yeast. While the weight curve rose thereafter it did so in an erratic and unconvincing manner from the standpoint of assuming that the antiscorbutic content of the Protein S.M.A. was inadequate. The previously described course of patient D. S. No. 3970 (chart Fig. 18), to whose Protein S.M.A. only yeast was added and no orange juice clearly emphasizes the correctness of this interpretation inasmuch as the weight curve of this patient was just as good as, if not a little better than, that of patient R. S., No. 3911 even after the addition of the fresh orange juice. Both patients were fed from the same lot of Protein S.M.A.

Intercurrent infections, some patent and some occult, in all probability are responsible for the development of this picture in scorbutic infants even though liberal quantities of the antiscorbutic vitamin have been administered and even though specifically scorbutic symp

toms disappear (See Fig 15, A Z, No 2094) McLean and McIntosh,¹⁰ who gave to all of their patients the large dose of 90 c c of fresh orange juice daily, have seen patients suffering from infections remain stationary in weight for weeks

Such observations indicate that, while the conclusions of the authors (Aron,¹¹ Nassau and Singer,¹² Abels,¹³ and Stern¹⁴) who have pointed out that dystrophy and dysergy which develop during the so-called latent stage of scurvy are responsible for the development of infections in scorbutic infants, are correct, there apparently are infections of another pathogenesis which develop and continue to persist in scorbutic infants even though the basis for the existence of the specifically scorbutic dystrophy and dysergy has been removed by the administration of the antiscorbutic vitamin in adequate and

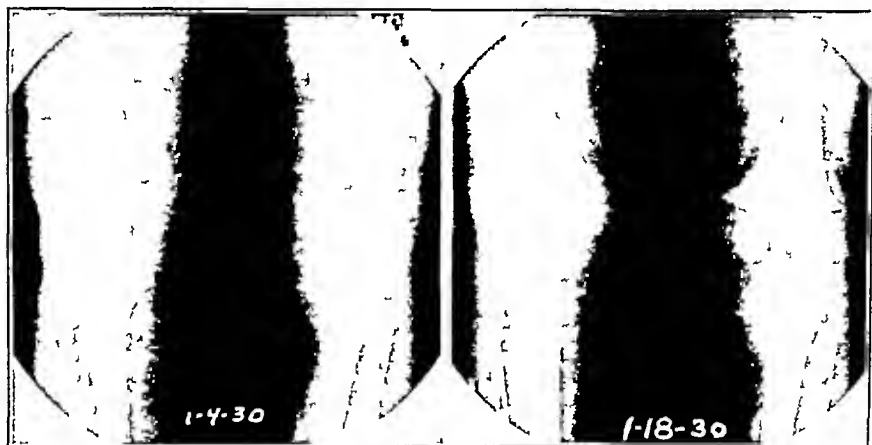


Fig 26

Fig 27

Figs 26 and 27—D S No 3970 (chart Fig 18) Fig 26 taken Jan 4 1930 Fig 27 taken Jan. 18 1930

very liberal doses during a sufficiently long period McLean and McIntosh also refer to such cases in their contribution

This is the principal reason, in our opinion, why the weight curves of all of the six scorbutic infants fed Protein S M A did not respond with a rather immediate and continuous upturn, as did patients R B, No 3774 (chart Fig 16) and G P, No 170 (chart Fig 13) Another factor, however, can be accepted as also having played a rôle in bringing about this result, namely, the age and weight of the infants at the time the antiscorbutic therapy was instituted. It will be seen that the infants presenting the best weight curves after the institution of Protein S M A feeding were relatively more underweight for their ages than were those whose weight curves did not do so well

It is clear from careful recapitulation of the data presented by the graphic charts and by the roentgenograms that enough of the anti-

scorbutic power of the 20 cc of lemon juice added to each liter of Protein S.M.A. at the time of manufacture remained to make it adequately antiscorbutic, even though periods of from five to twenty three months had elapsed since its manufacture. What might be called the best result was obtained with the Protein S.M.A. used for patient

Fig. 28.

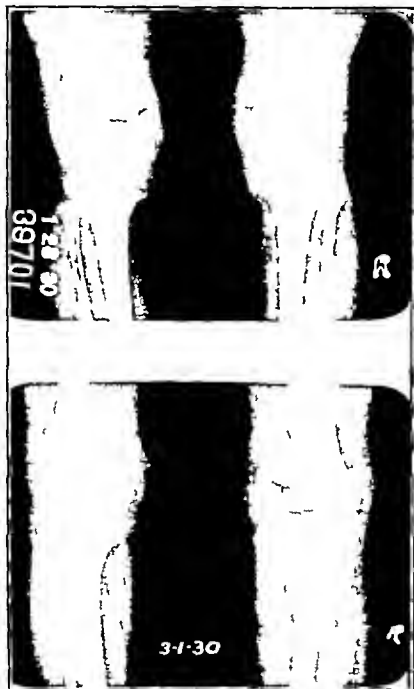


Fig. 29

Figs. 28 and 29—D. S. No. 3970 (chart Fig. 18) Fig. 28 taken Jan. 28 1930 Fig. 29 taken March 1 1930

G. P., No. 170 (chart Fig. 13), which was fifteen months old at the time of feeding. The oldest Protein S.M.A. twenty three months of age was fed to patient A. Z., No. 2094 (chart Fig. 15) and, while not so effective, did as well so far as the weight curve is concerned as did the subsequent additional daily administration of 60 cc of fresh orange juice, a finding which clearly does not warrant the conclusion

that the Protein S M A had lost its antiscorbutic power. As a matter of fact, the healing of the bones as demonstrated by the roentgenograms shows that the Protein S M A did retain antiscorbutic potency.

That the antiscorbutic potency of Protein S M A is retained to a satisfactory degree can be accepted from the difference in experience obtained with it and with regular S M A in the feeding of infants. We have never had a patient brought to us with scurvy who had been fed Protein S M A, whereas infants fed regular S M A have been admitted ill with scurvy. This difference undoubtedly is due to the difference in the content of the antiscorbutic vitamin in the two milks.

CONCLUSIONS

1 Fresh orange juice, spray dried as a constituent of a lactose orange juice mixture, was found to retain its antiscorbutic potency in a practically undiminished degree for at least fifteen months after its manufacture.

This conclusion was reached upon the basis of observations made on groups of scorbutic guinea pigs and on one very severe case of infantile scurvy.

The scorbutic guinea pigs were cured by the daily administration of an amount of the spray-dried orange juice equivalent to 3 c c of fresh orange juice, and the human infant by the giving of a daily dose equal to 45 c c of fresh orange juice.

2 Fresh lemon juice, spray dried as a constituent of Protein S M A, an acid protein milk to which are added at the time of manufacture 20 c c of lemon juice per liter, possessed, five to twenty-three months after its manufacture, antiscorbutic potency adequate to cure scurvy in six scorbutic infants, as judged clinically and roentgenologically.

The weight curves in the two infants who were decidedly underweight for their respective ages responded with an immediate, decided, and continuous upturn, whereas the weight curves of the four remaining infants who were not so much underweight did not so respond, even though the clinical and roentgenological symptoms of scurvy had disappeared. In two of these four infants additional administration of the antiscorbutic vitamin in the form of fresh orange juice did not alter the weight curve results at the time. Infections that were present in these infants on a non-scorbutic basis were accepted as the principal cause for the irregular weight curves produced.

The six infants received daily in the form of Protein S M A, which was taken as the infants' sole source of food and of vitamin C, at different periods the equivalent of 9 to 24 c c of lemon juice.

The lots of Protein S M A used were made at different periods between the years 1924 to 1930.

3 No case of scurvy in infants fed Protein S M A has so far come to our attention This finding further indicates that Protein S M A, is adequately antiscorbutic.

REFERENCES

- 1 Chick H Hume, E. M., and Skelton, R F Blochem J 12 131 1918
- 2 Givens, M H., and Cohen, B : J Biol. Chem 36 127, 1918.
- 3 Givens, M H., and McClugage, H B J Biol. Chem 37 233, 1919
- 4 Harden, A., and Zilva, S. S Blochem. J 12 259 1918
- 5 Harden, A. Zilva S S., and Still G F Lancet 1 17, 1919
- 6 Givens, M H., and McClugage, H B : Am. J Dis. Child 18 30 1919
- 7 Harden, A., and Robison R Blochem J 14 171 1920
- 8 Goss, H.: Hilgardia California Agrl. Exper Station 1 15 1920.
- 9 Bassett Smith F W Lancet 1 1102 19 0 Ibid 2 907 1920
- 10 McLean, S., and McIntosh, R Am J Dis. Child. 36 87 1921
- 11 Aron, H Klin. Wchnschr 1 2035 1922
12. Nassau E and Singer M J Jahrb f Kinderh. 98 44 1922.
- 13 Abels, H Ztschr f Kinderh 38 205 1923 Ergebn d inn. Med u Kinderh. 28 733 1924
- 14 Stern, R. Ztschr f Kinderh 38 32 1923
- 15 Gerstenberger H J., Smith D N., and Hacker G L. Tr Am Ped. Soc. 44 72, 1932.

DIPHTHERIA IMMUNIZATION WITH CONCENTRATED TOXOID INTRADERMALLY

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THE interval between the administration of the last dose of diphtheria toxoid and the development of immunity is approximately three months. It is true that many children are immune before this time¹ and also that a number are not immune at the end of this period, as has been amply demonstrated by Schick tests². We have, in this work, attempted to find a means of more rapid active immunization against diphtheria. We have tried to profit by the suggestions of Stewart and Rhoads,³ and by the subsequent work of Brodie and Goldbloom,⁴ where the superiority of the intradermal over the subcutaneous route in immunization against poliomyelitis was shown. The use of Lowenstein's ointment^{5, 6} and Schick with his intradermal B C G⁷ have also demonstrated the efficacy of the dermal route in the production of immunity. We therefore determined to test the value of concentrated diphtheria toxoid administered intradermally. The intradermal route has previously been attempted by Gorter and Hunink⁸ and Rohmer and Levy⁹ who used toxin-antitoxin mixtures, and also by Opitz¹⁰ who used toxin dilutions as well. Through the interest and cooperation of Doctors Fitzgerald and Fraser of the Connaught Laboratories of the University of Toronto, we have been supplied with concentrated toxoid prepared by precipitation with acetic acid in the cold. This concentrate was of such strength that 0.2 c.c. was the equivalent of 1 c.c. of ordinary toxoid as supplied for general use.

A preliminary group of twelve children, all Schick positive, was chosen, and injected intradermally, nine with 0.1 c.c. and three with 0.2 c.c. of this special toxoid. Four of these became Schick negative within six weeks, and one became Schick negative at the end of three months. Four remained Schick positive. Titrations of the antitoxin content of the blood were made in four of this group of twelve children. One child (M S.), who received only 0.1 c.c. of concentrated diphtheria toxoid intradermally and who became Schick negative within a week, showed three months later a blood antitoxin content of more than $\frac{1}{25}$ unit per cubic centimeter of blood, which is above the immunity level. Another child (H M.), who became immune at the end of six weeks,

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showed also more than $\frac{1}{25}$ unit at the end of two months. One other child, immunized in two months, showed more than $\frac{1}{10}$ unit. One child not immunized showed, four months after the injections, less than $\frac{1}{250}$ unit per cubic centimeter of blood. The ages of these children varied between one and one half and sixteen years, and seemed to bear no relation to their antigen forming capabilities. The details of this first experiment are shown in Table I.

TABLE I

NAME	AGE	DOSES	REACTION	POST SCHICK	INTERVAL	BLOOD ANTITOXIN
M S	6 years	1	3x4.6 cm.	Negative	7 days	$<\frac{1}{10} >\frac{1}{25}$
H H	18 months	1	1.6x1 cm	Negative	6 weeks	
H M	13 years	1	17x2 cm	Negative	6 weeks	$<\frac{1}{10} >\frac{1}{25}$
R O	11 years	1	—	Negative	6 weeks	
A. St J	11 years	1	None	Negative	6 weeks	
J S	9 years	2	1.5x2.5 cm.	Negative	12 weeks	
J I	10 years	1	Very severe	Negative	5 days	
C. C.	10 years	1	1x1 cm	Positive	1 week	
W H	7 years	1	None	Positive	3 months	
J L	5 years	2	None	Positive	4 months	$<\frac{1}{250}$
A. W	4½ years	2	1 cm.	Positive	3 months	
L. P. A.	16 years	1	8x4 cm.	Negative	2 months	$<\frac{1}{2} >\frac{1}{10}$

Twelve Schick positive children, 0.1 c.c. concentrated toxoid intradermally dose repeated in 2 children when first post. Schick was found positive.

This preliminary experiment demonstrated to us that rapid active immunization against diphtheria was possible. We therefore selected an other group of five older children, all Schick positive, and gave these children 0.2 c.c. intradermally of the concentrate (Table II) in a single dose. Four of these children became Schick negative one at the end

TABLE II

NAME	AGE	DOSES	REACTION	POST SCHICK	INTERVAL	BLOOD ANTITOXIN	REMARKS
R. M.	8 years	1	T 104 13x5 cm. desquamated	Neg	7 days	Before $<\frac{1}{100}$ After $>\frac{1}{10}$	
L. L.	9 years	2	2.5x2.5 cm	1st pos. 2nd neg	3 weeks	$<2 >1$	2nd dose gave severe reaction 5x6 cm. Schick neg 7 days after 2nd dose.
A. B.	13 years	1	4x8 cm T 103.2	Neg	16 days	>1	
S. R.	15 years	1	3.5x4 cm. severe local	Neg	2 weeks	>1	
J. T.	7 years	1	3x3 cm. papule	Neg	2 weeks	>1	

Five Schick positive children given 0.2 c.c. concentrated toxoid intradermally. One received a second dose when first post. Schick was positive. All immunized.

of seven days and three at the end of fourteen days. One child (L. L.), who was Schick positive at the end of two weeks, was given a second intradermal dose of 0.2 c.c., and one week later showed a negative

Schick reaction One boy (R M), who became Schick negative at the end of seven days, had a severe local and general reaction with temperature 104° and local erythema 13×5 cm Fourteen days after injection, his blood showed an antitoxin content greater than $\frac{1}{10}$ unit per cubic centimeter The other four children all showed a titer of more than one unit per cubic centimeter We relied on repeated Schick tests to tell us which children were immune and upon the estimation of the antitoxin content of the blood to tell us how much immunity they had developed *

That the Schick test itself, frequently repeated, may be a means of producing an antigenic reaction should be almost self-evident ^{11, 12, 13, 14} The Schick test is done by the intradermal injection of a small quantity of diluted but otherwise unchanged diphtheria toxin, and, in susceptible cases, this quantity is sufficient to produce a local inflammatory reaction which in itself is evidence of antigenic activity We found, for instance, that by repeating the Schick test in one Schick positive child at intervals of several days, the fourth Schick was negative, and the blood showed a titer above the immunity level In two other children so treated, the eleventh Schick was still positive in one and the twelfth in the other Thus, in three children given repeated Schicks, definite immunity was produced in one Fraser, in a private communication, has stated that the mere giving of the Schick test can act as a primary stimulus It was evident, therefore, that in order to test accurately the antigenic powers of the intradermal method with concentrated toxoid, the Schick test must be replaced by a method which itself is not antigenic For this reason we discarded anterior and posterior Schick tests in some of this work, and determined the state of immunity of the children, before and after inoculation, by means of directly estimating the antitoxin titer of the blood serum

We selected a group of ten susceptible children (Table III) as determined by antitoxin titers Six of these received a single dose of 0.2 c.c. of the concentrate intradermally Four of these showed antitoxin contents above the immunity level, one as early as two weeks after injection (M O), two in one month, and one in two months Two remained nonimmune Four children, all showing less than $\frac{1}{150}$ units of antitoxin per cubic centimeter of blood, received two doses of 0.2 c.c. each, one week intervening All showed titers above the immunity level, one at the end of eleven days, two at the end of three weeks, and one at the end of twenty-five days One child given 0.4 c.c. of the concentrate intradermally in a single dose (the equivalent of 2 c.c. of ordinary toxoid) showed immunity at the end of one month

*The first series of antitoxin titers was made by Dr. Donald Fraser at the Connaught Laboratories in Toronto. The other estimates were made in the Laboratory of the Children's Memorial Hospital in Montreal by one of us (D. L. K.)

There is apparently some relationship between sensitivity to toxoid and the rate of the antigenic reaction. Individuals highly sensitive to toxoid (i.e., sensitive to the protein of the diphtheria bacillus toxin) are easily and rapidly immunized¹⁵ those little or not sensitive to toxoid are more difficult to immunize. Forty-seven cases studied were divided into four groups according to the severity of the reaction after the

TABLE III

NAME	AGE	BLOOD ANTITOXIN	DOSE 0.2 C.C.	REACTION 1ST DOSE	REACTION 2ND DOSE	BLOOD ANTITOXIN	INTERVAL
G. P.	2½ years	<1/500 >1/600	1	0.3 cm.		>1/50	2 months
P. R.	8 years	<1/150	1	18 x 1.5		>1/50	1 month
M. O.	8 years	<1/150	1	0.3		>1/50	1 month
M. O.	8½ years	<1/150 >1/150	1	3.6 x 4		>1/50	2 weeks
A. W.	11 years	<1/50 >1/100	1	0.3		<1/50	2 months
J. Mc.	7 years	<1/50 >1/100	1	2		<1/50	1 month
J. G.	7 years	<1/50	2	2 x 3	5 x 4	<1/15	25 days
G. B.	7½ years	<1/50	2	0.3	7 x 4	>1/50	11 days
A. C.	9 years	<1/50	2	0.3	7 x 4	>1/50	3 weeks
J. B. G.	9 years	<1/50	2	2 x 3	3 x 7	<1/50	3 weeks

Second dose given one week after first dose.

administration of intradermal toxoid concentrate (Table IV). Those who had strong local and general reactions three in number, were all rapidly immunized after a single dose given intradermally as were twelve children who had strong local but no general reactions. Nine teen children gave weak local reactions, and of these only 57.8 per cent (i.e., 11) were immunized, while of thirteen children giving no local or general reactions only one was immunized (7.6 per cent).

TABLE IV

TYPE OF REACTION	NO. OF CASES	NO. IMMUNIZED	IMMUNIZED
Strong local and strong general reaction	3	3	100 %
Strong local reaction	12	12	100 %
Weak local reaction	19	11	57.8 %
No reaction	13	1	7.6 %

Another point observed in this work is one that has already been recognized by others, namely, that individuals with a moderately high titer—near, but below the immunity level—are very readily immunized,⁹ while those having extremely low titers are very difficult and sometimes impossible to bring up to the level of immunity. The same condition has, of course, been observed in the production of antitoxin in horses. Not all of them react in the same way in producing antitoxin. Some are very good antitoxin producers, and others less so.¹⁶ In this same connection, once a child has passed the immunity level it is quite easy to raise the antitoxin content of the blood to a very high titer¹⁷ by one

or two intracutaneous doses of toxoid. Thus a child showing $\frac{1}{6}$ unit per cubic centimeter of blood was readily raised to 2 units by a single dose

This work has been but the beginning of a somewhat different approach to the subject of diphtheria immunization in children. It is an attempt to develop a rapid method for active immunization, and the work done so far seems to point to the necessity of larger doses, and the importance of the production of sensitivity to toxoid in order to obtain good results. It is along these lines that the work is now proceeding. So far we have shown that under favorable conditions it is possible to immunize some children rapidly with a single or at most two doses of concentrated diphtheria toxoid, when given intradermally, and that the degree and rate of immunization probably depend upon the sensitivity of the individual to toxoid.

REFERENCES

- 1 Fitzgerald, J. G. *Ann Clin. Med.* 5: 870, 1927
- 2 Ramon, G., Dobré, R., and Mozer, G. *Compt Rend de L Soc de Biol de Paris* 107: 485, 1931
- 3 Stewart, F. W., and Rhoads, C. P. *J Exper Med* 49: 959, 1929
- 4 Brodie, M., and Goldbloom, A. *J Exper Med* 53: 885, 1931
- 5 Abt, A. F., and Feingold, B. F. *Am. J Dis Child* 41: 8, 1931
- 6 Kegel, A. H., and Gasul, B. M. *Am J Dis Child* 41: 45, 1931
- 7 Schick, B. *Acta Paediat* 11: 400, 1930
- 8 Gorter, E., and Huinink, A. T. B. *Arch de Med d Enf Paris* 23: 338, 1920
- 9 Rohmer, P., and Lèvy, R. *Arch de Med d Enf* 24: 585, 1921
- 10 Opitz, H. *Jahrb f Kinderh.* 92: 189, 1920
- 11 Glenny, A. T., and Allen, K. *J Hygiene* 21: 104, 1922
- 12 Glenny, A. T., and Hopkins, B. E. *Brit J Exper Path* 4: 283, 1923
- 13 Schwarz, E. *Pediatrics* 37: 32, 1929
- 14 Nasso, I. *Pediatrics* 33: 1141, 1925
- 15 Fitzgerald, J. G., Defries, R. D., Fraser, D. T., Moloney, P. J., and McKinnon, N. E. *Am J Pub Health* 22: 25, 1932
- 16 Schick, B. *N Y M J* 114: 197, 1921
- 17 Ramon, G., Debré, R., et al. *Am J Dis Child* 41: 1, 1931

MYELOPHTHISIS

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AT TIMES it is impossible, from clinical and even from hematologic examination, to differentiate between agranulocytosis, aplastic anemia, and some severe forms of thrombocytopenic purpura. The fever, the ulcerative and necrotic stomatitis or pharyngitis, the granulopenia, the rapid and fatal course characteristic of agranulocytosis, have all been observed in cases of aplastic anemia. Severe cases of thrombocytopenic purpura have been reported which presented clinical and hematologic findings that could easily lead one to make a diagnosis of aplastic anemia, similarly it is not unlikely that aplastic anemia may be mistaken for thrombocytopenic purpura, particularly in the early stages.

In a recent article on aplastic anemia¹ it was pointed out that there may be some relationship between these three diseases on the basis of bone marrow changes. This idea first suggested itself to me after I had the opportunity of studying the bone marrow in two fatal cases of hemorrhagic purpura and in one case of aplastic anemia. Opportunity has not been afforded me of studying the bone marrow in agranulocytosis, and therefore a description of bone marrow changes in a case of granulopenia in a child five years old, which was recently published by Kato and Vorwald,² will be cited.

Changes in the circulating blood elements as determined by the usual methods, are in reality indications of disturbances of the hemopoietic system in the great majority of cases, if not in all. i.e., diseases of the blood itself do not actually exist, changes may and do occur, but these changes are merely evidence that some disease or disturbance of the hemopoietic system exists. It is obvious therefore that the general term under which agranulocytosis, thrombocytopenic purpura and aplastic anemia are described as "diseases of the blood" is a misnomer, and that a clearer conception of these diseases would undoubtedly be obtained if they were described on the basis of bone marrow changes. Dameshek³ stated in a recent article that, since the blood platelets are derived from the megakaryocytes of the bone marrow, they should give, in association with the study of the number of reticulocytes and neutrophils, a complete index as to the activity of the bone marrow. In this paper the relationship of thrombocytopenic purpura, agranulocytosis, and aplastic anemia will be discussed from the point of view of bone marrow changes.

ESSENTIAL THROMBOCYTOPENIC PURPURA

CASE 1—D J, a female, was born at full term and normally delivered. Several hours after birth petechiae were observed on the skin and on the mucous membranes of the mouth, meconium containing some blood was passed. The capillary resistance test was strongly positive. Examination of the blood revealed the following: The bleeding time was twenty eight minutes, the coagulation time, four minutes, there was no retraction of the clot at the end of twenty four hours, the platelets numbered 18,000, there were 4,000,000 red cells and 12,000 white cells, the hemoglobin (Sahli) was 95 per cent. Otherwise the examination was negative. The infant was given 75 cc of whole blood intravenously, this was followed by a cessation of the bleeding from the intestinal tract and a gradual disappearance of the petechiae. Examination of the blood on the tenth day of life, the day of the infant's dis-

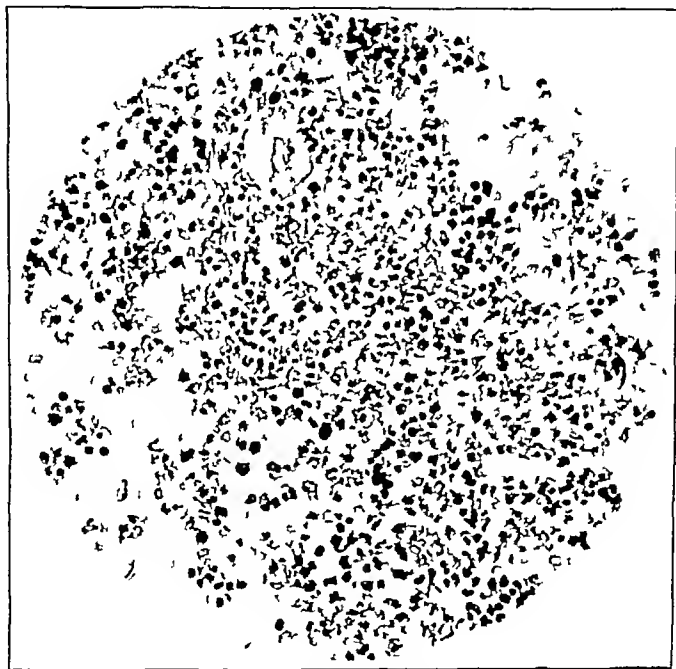


Fig 1—Case 2. Photomicrograph of the bone marrow, high power. The bone marrow is fairly cellular; the majority of cells consist of myelocytes, among which eosinophils are unusually numerous.

charge from the hospital, showed no marked changes from the initial findings. The child appeared well, no petechiae were present, but the capillary resistance test was still strongly positive. Unfortunately no detailed examination of the blood of the parents was made. The subsequent course of this patient's history is unknown.

CASE 2—The patient was a newborn male infant who, on the seventh day of life, manifested a purpuric eruption on the face, arms, and trunk, and on the lower extremities. The eruption was bright red, and varied in size from that of a pin head to that of a pea. There were also hemorrhages on the buccal mucous membranes. Blood was oozing from the circumcised area which had not healed entirely, and from the rectum. The spleen was not palpable. Otherwise physical examination was negative. Only one examination of the blood was made because the child died one and one half hours after it was first seen. The blood report was as follows:

red cells, 9,100,000 hemoglobin (Sahli) 22 per cent white cells 12,000, with 57 per cent polymorphonuclear leucocytes, 41 per cent lymphocytes 1 per cent myelocytes, and 1 per cent transitionals the coagulation time was thirty five minutes, and the bleeding time five minutes. There was no retraction of the clot at the end of twenty four hours. Only 30,000 platelets were present, the capillary resistance test was strongly positive, the Wassermann test was negative.

Necropsy revealed the following. The spleen was medium sized firm and dark red the liver was somewhat enlarged and firm and on section, had the appearance of nutmeg the heart was large particularly in its transverse diameter the left ventricle was a mere appendage to the right side of the heart the left auricle communicated freely with the right auricle.

Histologic description of the bone marrow. The bone marrow was fairly cellular with areas of excessive cellularity in which spaces between the bone trabeculae were densely jammed the large sinuses were engorged there were also many red cells in the meshes of the marrow the majority of the cells consisted of myelocytes among which the eosinophiles were unusually numerous mast cells were also fairly common. Among the reticulum cells there were some which stood out because of their unusually large size however they did not show any evidence of excessive phagocytosis. Other cells included mature polymorphonuclear leucocytes lymphocytes normoblasts and cells more embryonal in type which may be classed as myeloblasts or hemocytoblasts. Megakaryocytes were extremely scant and comparatively small. This applied particularly to the nuclei which were conspicuously hyperchromatic. Some of these cells had an oval or bean shaped nucleus which was different from that of the ordinary megakaryocyte. The cytoplasm of some of the cells was scant but in others fairly well developed. It stained plain blue and was devoid of the granules usually characteristic of the mature megakaryocyte.

CASE 3—D. A. a girl two years old, was brought to me on Oct. 6 1931 because of subcutaneous hemorrhages over the entire body and because of spontaneous bleeding from the mucous membranes of the mouth and nose. The mother stated that the purpuric spots first appeared when the child was three months old, and that at various intervals hemorrhages from the tonsils and from the nose occurred on one occasion there had been bleeding from the ear. Otherwise the past history was negative and unessential. Physical examination revealed purpuric spots on the lower part of the abdomen and on the lower extremities. The liver and spleen were not palpable. There was some oozing of blood from the left ear and from the right tonsil, the capillary resistance test was strongly positive. Hematologic examination at this time revealed a red cell count of 3,800,000; the platelets were 70,000 hemoglobin (Sahli), 62 per cent bleeding time twenty minutes; coagulation time four minutes. Whole blood, 50 c.c., from the mother was injected intramuscularly. Intramuscular injections of blood, in varying amounts were given from time to time. For a while improvement in the child was noticed. On January 11 1932 the child again developed severe bleeding from the nose and from the tonsils. Whole blood 40 c.c. from the father was injected intramuscularly, but with no apparent effect on the bleeding. Hospitalization was advised.

The child was admitted to the Israel Zion Hospital of Brooklyn on Feb. 1 1932. From Feb. 1 to Feb. 18 four transfusions were given at various intervals, in amounts ranging from 200 to 250 c.c. of whole blood. At no time did the child show any improvement. It may be seen from Table I that the platelets were always markedly reduced that the bleeding time was always prolonged and that at no time was there any clot retraction.

On Feb. 14 active bleeding from the lips and gums was present and an effusion in the right knee joint was noticed. Examination of the eyegrounds revealed retinal hemorrhages and blurred discs. A transfusion of 200 c.c. of whole blood was given.

on the same day. On the next day papilledema was definitely present, and a diagnosis of cerebral hemorrhage was made. Splenectomy was therefore advised. A preliminary transfusion was given and the spleen was removed, the child stood the operation well. Ten minutes after the operation the bleeding time was two and one half minutes, but the platelet count was still only 17,000. The child continued to show evidences of active bleeding, large tarry stools were passed, retinal hemorrhages were even more marked than previously, and there was active bleeding from the mucous membranes of the mouth and from the abdominal wound. On the day after operation the bleeding time was increased to thirty two minutes, and the platelet count to 30,000. On Feb 20, forty eight hours after operation, the child was again given a transfusion, on this day the platelets were 10,000, the bleeding

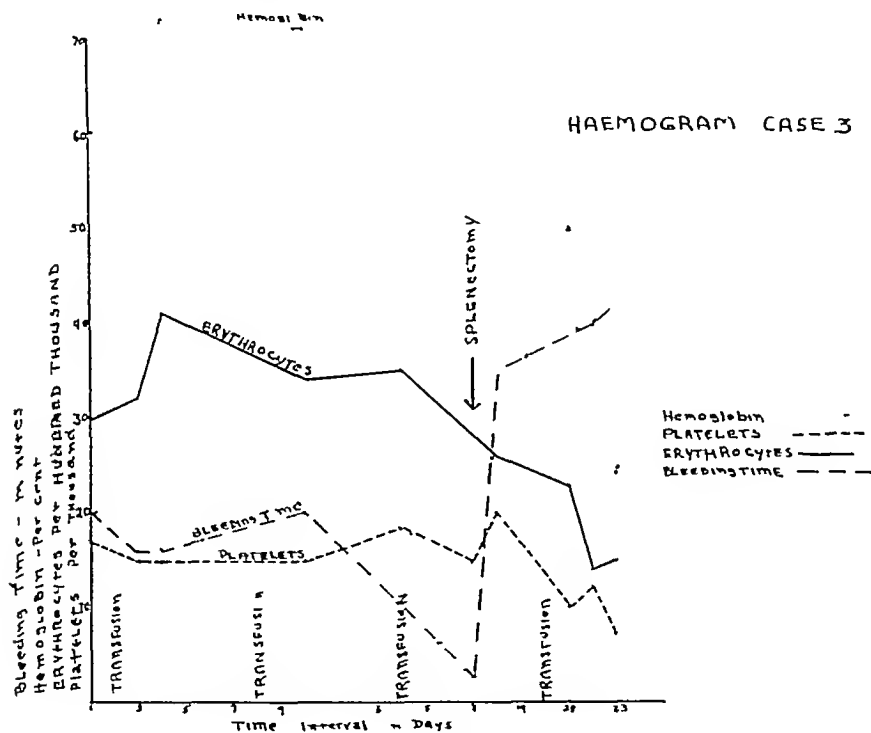


Chart I.

time was forty minutes, and there was no clot retraction. On Feb 24, the day of death, the child was practically exsanguinated. Drowsiness and clouding of the sensorium were present from Feb 14 until the day of death.

The necropsy report was as follows: The body was that of a white girl, poorly developed and poorly nourished, with marked pallor of the skin and of the mucous membranes. There was a surgical incision in the side, closed with sutures. There was a large collection of clotted blood underneath the dura mater in the occipital region. Both lungs were free and contained air throughout, they were pale, with the exception of the posterior portion of the left lower lobe, which was slightly bluish red and somewhat firm to the touch. The heart was of average size and well contracted. The valves were thin and smooth. Both leaflets of the diaphragm were dark red. Incision revealed a diffuse infiltration of blood within the muscle tissue underneath the peritoneal covering.

TABLE I
BLOOD FINDINGS IN CASE 3

DATE	2/2/32	2/4/32	2/6/32	2/11/32	2/15/32	2/19/32	2/10/32	2/22/32	2/23/32	2/24/32
Erythrocytes	3 000 000	3 200 000	4 100 000	3 400 000	3 500 000		2 600 000	2 300 000	1 400 000	1 400 000
Hemoglobin	60%	64%	80%	73%	74%		02%	50%	50%	55%
Platelets	17 000	15 000	15 000	15 000	19 400	17 000	20 000	10 000	12 000	7 000
Bleeding time	20 min.	16 min.	10 min.	20 min.		2½ min.	35 min.	40 min.		40 min.
Coagulation time	7 min.	0 min.	3 min.	3 min.			4 min.	10 min.		9 min.
Clot retraction	0	0	0				0	0		0
Leucocytes	8 000	4 000		0 000			4 000	4 600		8 000
Polymorphonuclear leucocytes	65%	64%		52%			07%	54%		63%
Lymphocytes	30%	32%		15%			27%	41%		30%
Eosinophils	3%						1%			
Monocytes	2%	4%		6%			7%	6%		7%

Transfusions--on 2/2 3/8 2/14, 2/10
 Splenectomy on 2/18

There was a large amount of clotted blood in the abdominal cavity covering the surface of the intestines. The muscles of the abdominal wall showed similar dark red patches of bloody infiltration as in the diaphragm. The spleen was absent. The stomach contained a large amount of dark red mucous material, and the mucosa was dark brown. The liver was medium sized and pale grayish in color. The cut surfaces showed no traces of the ordinary acinous structure. The kidneys were of medium size, firm, and yellowish gray in color.

Pathologic diagnosis Splenectomy for thrombocytopenic purpura, diffuse intramuscular, intraperitoneal, subdural, and gastric hemorrhages. Anemia.

Histologic report Bone marrow—the medulla was loose and fairly cellular, many myeloid cells were present, but no megakaryocytes were visible.

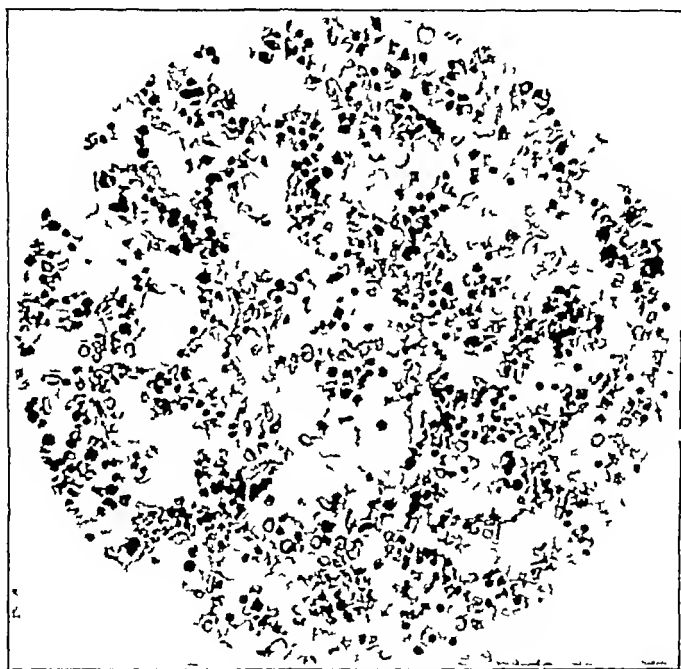


Fig. 2—Case 3. Photomicrograph of the bone marrow, high power. The medulla is loose and fairly cellular; many myeloid cells are present; no megakaryocytes are visible.

In a discussion of essential thrombocytopenia there are many points of importance, among which is the question of whether there is a congenital form of thrombocytopenic purpura. In the last few years a number of cases have been reported in which newborn infants showed evidence of this disease immediately after birth (Leschke,⁵ Liebling,⁶ Waltner,⁷ Rushmore,⁸ Gutfreund,⁹ Dohrn,¹⁰ Greenwald and Sherman⁴) and Case 1 in this paper. The mothers of six of these patients also suffered from the disease. In view of this fact it is likely that there is a congenital or hereditary factor in some of the cases of essential thrombocytopenia. This view is substantiated by the histologic findings of the bone marrow in Case 2 and in Gutfreund's case.

Gutfreund's patient showed hemorrhages of the skin at birth, and on the second day of life vomited blood. Hematologic examination revealed no platelets, a bleeding time of forty minutes, no retraction of the clot and a coagulation time of six minutes. Examination of the mother's blood showed 32 000 thrombocytes. The infant continued to bleed from time to time in spite of repeated transfusions, and died at the age of four months. At necropsy the bone marrow showed many fat cells but no megakaryocytes. Although the disease may be congenital, active manifestations may appear only at intervals of weeks, months, or even years.

One of the most distinctive features in purpura hemorrhagica is the change in the quality and quantity of the platelets. Four possibilities have been mentioned to account for the reduction in platelets. The first is the destruction of areas in the bone marrow concerned with the production of megakaryocytes as a result of myeloid hyperplasia, this is probably a mechanism for the reduction of platelets in leucemia and need not be considered in this discussion. The second possibility is the failure of production of megakaryocytes because of bone marrow deficiency with the resulting disappearance or marked diminution of the platelets, changes in the morphology of the megakaryocytes, as for example, the absence of the azure granules, probably account for the change in the quality of the platelets. The third possibility is the excessive destruction of platelets in the spleen. The fourth is that the spleen produces a hormone or some toxic substance which depresses bone marrow function and has a selective action on the megakaryocytes. (See Frank,¹¹ Kretz,¹² Hirschfeld,¹³ Klemperer,¹⁴ all quoted by Brühl¹⁵)

At first glance it would seem that the question of whether there is a deficient production or an increased destruction of platelets could have been decided by careful studies of the bone marrow and of the spleen. In reviewing the literature however it is remarkable to observe how few studies of the bone marrow have been made in spite of the fact that a large number of cases of essential thrombocytopenia have been reported. Studies of the bone marrow have been made by Lantier, Oberling and Worringer,¹⁶ Forster,¹⁷ Frank,¹¹ Kaznelson,¹⁸ and Wiener.¹⁹ All the authors mentioned found large numbers of megakaryocytes except Lantier, Oberling and Worringer, who found an absence of megakaryocytes in a boy five years old who died one week after splenectomy—a case similar to Case 3. Stern and Hartman,²⁰ however, found definite morphologic changes in the megakaryocytes on sternal puncture particularly an absence of azure granules. In two of the cases here presented examination of the bone marrow showed no megakaryocytes in one and only few megakaryocytes with morphologic changes in the other. In neither of these cases was there any evidence of excessive destruction of platelets in the spleen. While

it is difficult to draw definite conclusions from three or four cases, it is not illogical to assume that the thrombocytopenia in some cases of purpura hemorrhagica is based on a deficiency of the bone marrow which may well be congenital

Kaznelson¹⁸ recommended splenectomy for the cure of essential thrombocytopenic purpura because of his belief that the thrombocytopenia is due to a primary hyperfunction of the spleen with an increased destruction of the platelets. Since then many reports have appeared substantiating the excellent results obtained by Kaznelson with splenectomy. Occasionally, however, cases have been reported that did not respond to splenectomy, for example, McLean et al.,²¹ Kasdoba,²² Lautier, Oberling and Worringer,¹⁶ Blumfield,²³ Jones and Tocantins,²⁴ Case 3 in this paper. In studying these reports one is impressed by the fact that the failure with splenectomy occurs in very young children. Piney²⁵ has divided the results of splenectomy into three groups. The first is that in which there is a rapid and persistent rise in the platelet count to normal figures, the second is that in which there is a rise after operation, but a drop later, and the third is that in which there is no increase in the platelet count, such as occurred in Case 3. This substantiates the belief that has lately become prevalent that the platelet count alone should not be used as an indication for the removal of the spleen.

In view of the foregoing, is it not possible that each of the three opinions may be correct at one time or the other, namely, first that there is a deficient production of platelets because of a congenital inferiority or insufficiency of the bone marrow, second, that there is an increased destruction of platelets in the spleen, and third, that the spleen inhibits the production of platelets. In other words, it is not improbable that there are two types of thrombocytopenic purpura. The first occurs in infants who are born with a deficient bone marrow, which in itself is not enough perhaps to produce active manifestations of the disease, and that some toxic or unknown agent, which has no effect in a child with normal bone marrow, produces the typical picture of purpura hemorrhagica. The patients belonging to this group will not respond to splenectomy. In the second type the bone marrow functions normally, i.e., a normal number of megakaryocytes of good quality is produced, but the platelets are destroyed in the spleen itself, or, as Frank¹¹ believes, the function of the bone marrow which was previously normal, becomes depressed or inhibited by some hormone or toxic substance produced by the spleen. It is in the patients of this group that the brilliant results from splenectomy are obtained.

In both groups the toxic agent which is the exciting factor probably has a destructive action at the same time on the capillary walls producing increased permeability which is mainly responsible for the spontaneous bleeding. This view probably explains the findings of

many observers that there is no relationship between the severity of the disease and the platelet count. As a matter of fact, it is Brühl's¹⁶ opinion that the most important factor in the production of active bleeding in purpura hemorrhagica is the increased permeability of the capillaries. This opinion was also expressed by Jones and Tocantins¹⁴ who stated that capillary hyperpermeability or capillary weakness is essential for the production of hemorrhagic phenomena which may appear if this condition is present alone or if both capillary hyperpermeability and platelet deficiency are found. On the other hand, Lescher and Hübner¹⁷ stated that the relative importance and the possible interaction of platelet and capillary in the production of hemorrhages are not fully settled. They point to the fact that increased capillary permeability cannot be the primary cause of hemorrhage, since such blood disorders as aplastic anemia, in which there is simply a bone marrow deficiency with diminished production of the blood elements, show no suggestion of capillary affection. Finally, it is suggested that bone marrow punctures be made in cases of thrombocytopenic purpura to determine the presence or absence of megakaryocytes.

AGRANULOCYTOSIS OR GRANULOPENIA

Agranulocytosis is uncommon in childhood. Recently Kato and Vorwald⁸ reported the case of a female white child, five years of age, who appeared acutely ill and moderately emaciated when first seen. The posterior pharyngeal wall had some small ulcers surrounded by a dirty exudate, ulcers of the mucous membranes were also present on the cheeks and under the tongue, the cervical glands were not enlarged. Otherwise physical examination was negative except for the presence of a pneumonic process over the left lobe posteriorly. The child was under observation from May 30, 1931 until death, which occurred on June 2, 1931. The most characteristic abnormality was the blood picture which showed a leucopenia ranging from 550 to 900 white cells. Only on the day of admission were granulocytes seen. The differential count on this day was: Neutrophils leucocytes, 16 per cent, eosinophiles, 0, basophiles 0.8 per cent, myelocytes 0.8 per cent, lymphocytes 96 per cent. On the two subsequent days of the child's stay in the hospital no granulocytes were observed. Erythrocytes ranged in number from 3,250,000 to 3,750,000. The hemoglobin (Newcomer) content was 51 to 56 per cent. The platelets were 170,000.

These authors differentiated essential agranulocytosis from symptomatic agranulocytosis and stated that while the former is rare, only five cases having been reported up to the time their report was published the latter is common. The bone marrow in their patient showed but slight activity, all the elements found were mainly hemocytoblasts, the mature myelocytic elements were scanty, occasionally

a promyelocyte was found, but myelocytes, mature basophilic, eosinophilic, and neutrophilic leucocytes were almost entirely absent. Megakaryocytes were fairly numerous.

Kastien²⁷ stated that the symptomatic type, in which evidences of a severe infective process are usually found, is due to a peculiar specific reaction of the bone marrow to a toxic agent. Harkins²⁸ also divides the cases into two groups, as follows:

- 1 Primary granulopenia
- 2 Secondary granulopenia, due to
 - a Chemical poisonings
 - b Radiation
 - c Sepsis
 - d Blood diseases—aleucemic leucemia, aplastic anemia

He concludes his classification, however, with the statement that it is possible that eventually all cases will be considered secondary.

Recently Weiss and Goldbloom²⁹ described a symptom complex somewhat similar to that described by others as agranulocytosis, which they termed dysplastic granulocytemia. It is characterized by a primary involvement of the granulopoietic system with the resultant production and distribution of imperfectly constructed neutrophils.

The points that are still open to question, as far as classification and etiology are concerned, are: First, is granulopenia a primary disease due to an unknown virus or to a toxic agent associated with the Benzene ring (Kracke³⁰) with specific affinity for the myeloid system, or second, is it a syndrome which may occur in the course of any septic process when toxins attack the bone marrow, the resulting symptoms depending on the duration and the intensity of the toxic agent, or third, is there some endogenic factor, for example congenital weakness of the bone marrow, at fault and would a toxic agent which produces no effect on the myeloid system in a normal individual produce granulopenia with all its severe manifestations in an individual with a congenital deficiency of the marrow? The fact that some patients present a previous history of leucopenia, as was recently reported by Harkins,³¹ would speak for the last viewpoint.

The points that are well established and that should be emphasized are: First, that the decrease in the granulocytes in the blood is due not to excessive destruction in the circulation but to deficient production in the bone marrow, body defense is lowered because of the marked decrease or absence of leucocytes in the circulation, which fact accounts for all other manifestations including the necrotic lesions of the mucous membranes. Histologic examination of the bone marrow at necropsy or examination of the bone marrow during life (Kastien²⁷) shows quite regularly a cell poor marrow with practically no granulocytes. This is true of both groups of cases. Fitz-Hugh and

Krumbhaar,²² however, reported one case of agranulocytosis with myeloid cell hyperplasia in the bone marrow

In other words, regardless of whether the disease is primary or not, or whether an infective process can be demonstrated or not, the disease or syndrome does not occur unless a deficiency of the bone marrow is present. Whether this deficiency is based on a congenital, weak myelopoietic system or not is a problem which does not lend itself to solution at the present time. It is obvious therefore that the terms "granulopenia," "agranulocytosis," or "granulocytic angina" are misnomers and that each term describes but a single phase of the disease.

APLASTIC ANEMIA

It is now generally conceded that aplastic anemia is a disease *sui generis* and is not a biologic variation of some form of primary or secondary anemia. The disease is characterized by its rapidly and progressively fatal course. In no true case has the patient been known to recover. The two outstanding features of the disease are the severe anemia and the hemorrhagic diathesis which manifests itself by hemoptysis, epistaxis and purpuric eruptions. The blood picture is of course the main point of clinical diagnosis. There is a marked decrease in the hemoglobin content with a diminution of the red cells to a million or less, the hemoglobin is reduced to 10 or 15 per cent, the color index is approximately 1, nucleated red cells, reticulocytes and polychromatic erythrocytes are absent, there is a decided leucopenia with a reduction of the neutrophilic leucocytes and an almost complete absence of eosinophiles. Thrombocytopenia is constant and is a feature of the disease.

There are two types of aplastic anemia: first, the primary or essential and second, the symptomatic. In this paper only primary or idiopathic aplastic anemia is discussed. The most generally accepted explanation is that the disease is due to a primary lesion of the bone marrow. Frank²³ expressed the opinion that the disease results from a primary aplasia of marrow by some unexplained toxic action on the marrow itself and that there is a simultaneous disappearance of erythrocytes, granulocytes, and platelets. This theory explains his preference for the term 'panmyelophthisis'.

Hirschfeld,²⁴ Pappenheim,²⁵ Türk,²⁶ and Nagel²⁷ are of the opinion that aplastic anemia results from a congenital or acquired deficiency and that any sort of infection or intoxication produces the symptoms characteristic of the disease. The following case¹ briefly cited here bears out this opinion to some extent. The disease appeared to be initiated by the advent of an upper respiratory infection and aggravated by one dose of toxin antitoxin.

REPORT

S B, a girl of Jewish extraction, was born at full term and normally delivered. She was well until sixteen months of age, when she had an attack of tonsillitis. On Feb 9, 1932, immediately following the attack, the mother noticed that the child looked pale and, on the advice of her family physician, sent the child to a hospital where it was found that the hemoglobin content of the blood was 31 per cent. A transfusion was given, and the child was discharged several days later as improved. The child was apparently in good health until May 15 when an injection of toxin antitoxin was given. This was almost immediately followed by an elevation of temperature to 102° F, and the arm, at the site of the injection, became red and swollen. The mother noticed a change in the color of the patient and said that the skin was a muddy brown. The child was then readmitted to the hospital for treat-

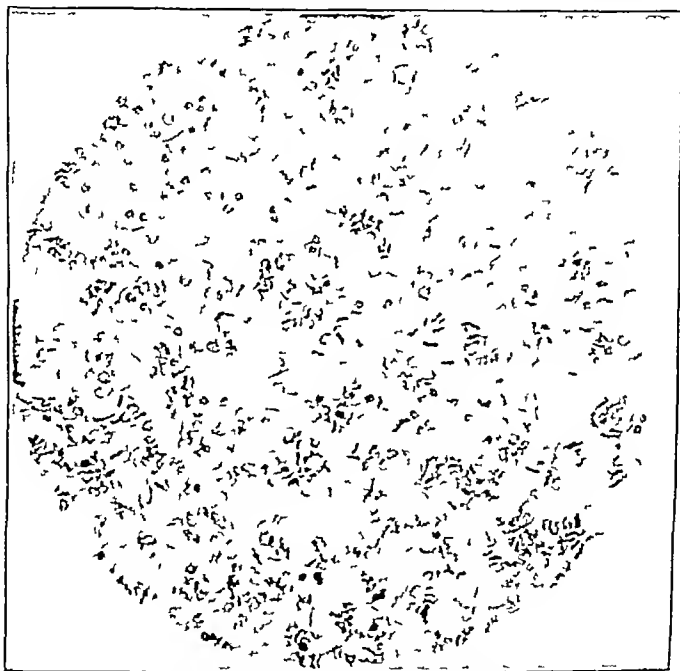


Fig 3—Photomicrograph of the bone marrow high power. The meshes of the reticulum degenerating red cells one megakaryocyte and a few other cells mostly lymphocytes.

ment and another transfusion was given. The general condition, however, became worse and, against the advice of her physician, the patient was removed to her home. At this time, June 5, I was asked to see the child. Examination revealed a sick child whose sensorium was clear, but who was apathetic. The skin had a dirty brown appearance, but the lips and finger nails were almost white. The conjunctiva and the mucous membranes of the mouth appeared bloodless, an ulceration of the pillar of the left tonsil which bled rather freely was present. Petechiae were present over the flexor surfaces of both arms, the capillary resistance test was strongly positive. Examination of the blood showed the following: red cells, 750,000, hemoglobin (Sahl), 10 per cent, white blood cells, 22,000, of which there were 8 per cent polymorphonuclear leucocytes, 80 per cent lymphocytes, and 12 per cent lymphoblasts. The platelets numbered 25,000, there was one reticulocyte in 2,000 red cells, the bleeding time was ten minutes, and the coagulation time four minutes.

The patient was given 200 c.c. of whole blood intravenously on several occasions. She was fed fresh bone marrow first by gavage and later by mouth. Temporary improvement occurred so that there was a distinct remission in the disease which lasted about two months. On Sept 7 the patient was readmitted to the Israel Zion Hospital of Brooklyn in a moribund state. In addition to the evidences of a severe anemia there were signs of consolidation of the lower lobe of the left lung. On the following day the child had a convulsion which lasted fifteen minutes this was followed by coma which persisted until death on the same day.

Examination of the blood on the day before death Sept 7 showed the following: red cells, 1,700,000; hemoglobin (Sahli) 30 per cent; leucocytes 6,000 with 1 per cent polymorphonuclear leucocytes, 89 per cent lymphocytes and 10 per cent lymphoblasts. There were 20,000 platelets, and 1 reticulocyte in 1,000 red cells.

A complete necropsy was performed but only the bone marrow findings will be cited here. The bone marrow in the sternum was dark red, and when the bone was cut, much blood oozed out. The marrow of the tibia was abundant dark red, and quite firm. Histologic examination. The marrow in the long bones, as well as in the ribs, showed enormous congestion with red cells while between the vessels edema was prevalent. In addition to the endothelial cells lining the blood vessels only scanty cells were present most of which were polymorphonuclear leucocytes. There were also occasionally large cells of the size of megakaryocytes with one single oval or irregularly shaped nucleus. Many of the polymorphonuclear cells seemed to be degenerating. There were also a few reticulum cells with normally shaped nuclei. Myelocytes were found in places but they were much less numerous than the polymorphonuclear cells.

The most constant and striking pathologic change in aplastic anemia is a fatty yellow appearance of the bone marrow. The presence of a red bone marrow, however, should not lead one to discard the diagnosis of aplastic anemia until careful histologic study has been made. In this patient, while the bone marrow appeared red on gross examination microscopic examination revealed that this color was due to hemorrhage and that there was an almost complete absence of cellular elements.

That an acute infection may be the starting point of the disease has been observed by several authors (Smith²⁶ Greenwald¹). It seems, however, that some other factor must be concerned in the pathogenesis of primary aplastic anemia or many more cases would occur. It is not unlikely that a congenital inferiority of the bone marrow is present from birth, and that an infection or a toxic substance which in a normal person would produce only mild and temporary changes in the bone marrow, is sufficient to bring about the severe, permanent, and more or less widespread changes characteristic of aplastic anemia. Changes in the blood picture pointing to an insufficiency of the bone marrow have been found in other members of a family in which the disease occurred (Bickel²⁷).

Thus it is evident that definite bone marrow changes are present in these three diseases and that deficient production of one or of the other or of all the blood elements normally produced by the marrow is encountered. Lesch and Hubble²⁸ suggested that each element

has its appropriate regulator, but the fact that intermediate cases occur makes it equally certain that the regulatory factors are not rigidly selected for only one element. They believe that the deficiency in the bone marrow occurs because of a deficiency in the controlling factor. This point of view is purely hypothetical, as is the point of view expressed in this paper, that aplastic anemia, agranulocytosis, and some forms of thrombocytopenic purpura occur primarily because of a congenital defect of the bone marrow. Further investigation may reveal the accuracy or fallacy of one or of the other or of both of these hypotheses. So too, the question as to whether these three conditions are distinct and separate diseases or whether they are closely related and are possibly variants from an identical origin does not bear discussion because of our limited knowledge. A fact that is not hypothetical and that is worthy of emphasis is that the three diseases resemble one another in the clinical and blood pictures, and particularly in the bone marrow changes.

The difficulty that arises in classifying diseases when the nomenclature is based only on one sign or on one symptom may be seen from the following. Bigler and Biennemann,³⁸ in their report of a series of cases of agranulocytosis, included a number that were unquestionably cases of symptomatic aplastic anemia. In six cases there was a simultaneous and gradual reduction of red cells, platelets, and granulocytes. Indeed the authors stated that their cases seemed to coincide in clinical course and in blood picture with the group classified as aplastic anemia, but the fact that the bone marrow was red instead of yellow caused them to abandon the diagnosis of aplastic anemia. The error of such a conclusion has been pointed out by several authors (Baar and Stransky,³⁹ Greenwald,¹ and Lindquist⁴⁰). That Bigler and Biennemann were cognizant of the fact that the present classification leaves much to be desired and that there may be some relationship between the diseases may be seen from their conclusion in which they stated: "From a study of our cases and of the literature it seems that there is no one etiologic agent that can produce the condition described here, but that any one of several by their action may produce a similar condition, varying as to clinical picture and to blood picture according to the part of the hemopoietic system affected, the erythrocytic and granulocytic, the lymphatic or thrombocytic."

Whether each bone marrow element has a special regulator, as Lescher and Hubble²⁶ believe, or whether one or several etiologic agents operate to produce these diseases, the fact remains that a nomenclature based on pathologic changes is certainly more desirable than one based on a single sign or symptom. It seems to me that the term "panmyelophthisis" for aplastic anemia, as Frank¹¹ originally suggested, and the terms "granulophthisis" and "thrombophthisis" for agranulocytosis and thrombocytopenic purpura respectively, as

Lescher and Hubble²⁶ suggested are to be preferred to the present terms. It is also suggested that the term 'thrombolytic purpura,' first employed by Kaznelson be adopted for the cases of thrombocytopenic purpura in which the reduction of platelets is due to an increased destruction by the spleen. For the differentiation of these two types of purpura bone marrow puncture as suggested before, is necessary.

REFERENCES

- 1 Greenwald. Am J Dis Child (In print)
- 2 Kato and Vorwald. Am J Dis Child. 44 5. 6 1933
- 3 Dameshek: Arch. Int. Med 50 5:9 1932
- 4 Greenwald and Shermann. Am. J Dis Child 38 1245 1930
- 5 Leschke. Frgeln d ges Med. 9 344 1906
- 6 Liebling, P. Am J Obst & Gynec 11 84, 1926
- 7 Waltner K. Jahrb f Kinderh. 106 30, 1904
- 8 Rushmore S. Am J Obst & Gynec 10 603 1927
- 9 Gnttfreund. Monatschr f Kinderh 45 436 1933
- 10 Dohrn. quoted by Gnttfreund (9)
- 11 Frank. Die hemorrhagischen Diathesen in Schittenhelm's Krankheit des Blutes und Blutbildende Organe Berlin 1900 Julius Springer
- 12 Kretz. quoted by Brühl (15)
- 13 Hirschfeld. quoted by Brühl (15)
- 14 Klemperer. quoted by Brühl (15)
- 15 Brühl: Ztschr f Kinderh. 54 160 1933
- 16 Lautler Oberling and Woringer. Rev franc de pediat 3 340 1927
- 17 Furator A: Ztschr f klin Med 92 170 1921
- 18 Kaznelson. Ztschr f klin Med 87 133 1910
- 19 Wiener. quoted by Brühl (15)
- 20 Stern and Hartman. Ztschr f klin Med 104 409 1926
- 21 McLean, Kreidel and Caffey: J A M A 98 387 1930
- 22 Kasdoba. Arch f klin. Chir 168 794 1931
- 23 Blumfeld. Internat. Clinics 3 179 1931
- 24 Jones and Tocantins. J A. M. A 100 97 1933
- 25 Piney. Recent Advances in Hematology London 1931 p 100
- 26 Lescher and Hubble. Quarterly J Med (New Series) 1 420 1932.
- 27 Kastlen. Am J M Sc. 173 710 1927
- 28 Harkins H N. Arch. Int. Med 47 408 1931
- 29 Weiss and Goldbloom. Am J of Clin. Path 2 220 1930
- 30 Krucke. quoted by Harkins (29)
- 31 Harkins, H N: Arch. Int. Med. 47 408 1931
- 32 Fitz Hugh and Krumpholtz. Am. J M Sc 183 104 1932.
- 33 Pappenheim. quoted by Baar and Stransky (39)
- 34 Türk. quoted by Herman. Am. J Dis. Child 23 484 1932.
- 35 Nagell. quoted by Baar and Stransky (39)
- 36 Smith L. W. Am J Dis. Child. 17 174 1910
- 37 Blekel. Wiener klin. Wchnschr 42 1286 1929
- 38 Bigler and Brennemann. Am J Dis. Child. 40 515 1930
- 39 Baar and Stransky. Die klinische Hematologie des Kindesalters F. Deuticke 1928
- 40 Lindquist. Monatschr f Kinderh 55 407 1933

FETAL AND NEONATAL MORTALITY

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THIS age-old subject has been discussed and argued over until it is worn threadbare and yet it seems to me that there is still something to be said about it. During the last few years and especially since the White House Conference, there has been a renewed interest in the newly born infant, and in attempts to reduce neonatal deaths. It is therefore, perhaps not untimely to consider again the question of mortality before and just after birth. With the experience which we have had within the past two decades in the reduction of mortality in infants past this age, we are likely to think that the approach to the problem in the newborn and fetus will be just as easy and the results to be obtained will be just as striking. Perhaps no method of approach to this subject is better than that of a consideration of the causes of our failures in those periods of existence. Certainly we must confess that we approach the subject of reduction of mortality at this stage of development with much less knowledge of disease and of life processes than that which we possess for the older infant, no matter how inadequate that may be.

Inheritable factors in the wide sense of the term have much to do with disease as we see it in adults and in children. Certain conditions and certain differences can only be accounted for on this basis. Why, for instance, two children growing up under practically identical conditions should differ as to hemoglobin content in their blood is one of the things which can only be accounted for by presupposing a fundamental and inherited difference in the iron metabolism of the two individuals. That this factor plays a very definite rôle in the mortality of the fetus and newly born child has received comparatively scant recognition. That this rôle may be of varying degree is a thing which has scarcely been considered. Let us attack this problem then from two standpoints. First, the inherent inheritable factor and second, noninheritable factors which have to do with disease and trauma. We must always remember that to draw a sharp line between the two is impossible. Inherited predispositions will invariably have an effect upon disease and to a certain extent upon trauma. Disease and trauma may, on the other hand, be determining factors too, when inherited taint plays a predominant rôle. A statement of Streeter in a recent monograph sums up these ideas:

"It is now well known that eggs, and by eggs I refer to fertilized ova, are not all of equal quality. In pigs and in man it is estimated

that as many as 25 per cent of them are not good enough to be born as living individuals. The failures are found in the uterus arrested in various stages of development in proportion to the degree of their poor quality. In man such specimens make up a large part of the material that the physician encounters in miscarriages. Nor is the importance of quality limited to uterine life. Whether the infant survives its first year—and in fact a large number of them fail to do this—depends in considerable part on the original quality of the egg. If they withstand the usual experiences of life until between 50 and 60 years and then succumb to its aggregate wear and tear, they conform to the actuary's expectation of life at birth and to the embryologist's expectation to the performance of an egg of average quality. It is only the extraordinarily good egg that is still going strong at 80 years, and we see him (or her) do this in the absence of any exquisite hygienic regime or environmental favor."

Let us approach this subject from the standpoint first, of fetal deaths and then of neonatal deaths. In a recent article by Gillespie¹ the cause of death in 338 cases of stillbirth is discussed and I am repeating here the table (Table I) which is contained in that article. So far as I know this is the most recent attempt to discuss this subject and while there may be many others there is no particular advantage in a large mass of statistics. Slight variations of course may be expected, but the main causes of fetal deaths remain very much the same and for the purpose of this paper we are not so much interested in minor changes as we are in large groupings.

If we divide the groups under the two headings mentioned above we shall find that under the first heading or the inherited factors, the following will unquestionably come

Prematurity	54 cases	15.97%
Malformation	37 cases	10.94%
Fetus Papyraceous	1 case	0.29%
Oligohydramnios	1 case	0.29%
Intrauterine deaths (macerated)	54 cases	15.97%

This makes a total of 147 deaths (43.46 per cent)

Those belonging to the second category may be mentioned as—

Syphilis	18 cases	5.32%
Prolapse of the cord	9 cases	2.66%
Trauma at birth	101 cases	29.88%
Difficult labor	2 cases	0.59%
Asphyxia	1 case	0.29%
Meningitis	1 case	0.29%

This makes a total of 132 deaths or 39.03 per cent. In other words the conditions which are frankly to be classed in the inheritable causes are greater than those which are to be classed in the non-inheritable causes. Of the total number of 338 cases of death, in 13 the cause was undetermined. This leaves a balance of 46 which were

TABLE I
CAUSES OF DEATH IN 338 CASES OF STILLBIRTH (GILLESPIE)¹

CAUSE OF DEATH	MALES	FEMALES	TOTAL	PER CENT	AGE, MONTHS									
					LESS THAN 5	5 6	6 7	7 8	8 9	9 10	10 AND MORE	UN KNOWN		
Stillbirth	180	158	338	---	1	10	34	42	43	59	101	46		
Syphilis	11	7	18	5.32	--	--	1	3	4	7	--	3		
Toxemia of pregnancy	6	9	15	4.42	--	--	1	4	3	3	--	1		
Placenta previa	4	7	11	3.25	--	--	--	--	3	2	5	1		
Abruptio placentae	9	3	12	3.55	--	--	--	2	1	4	4	1		
Prolapse and compression of cord	4	5	9	2.66	--	--	1	--	1	3	4	--		
Prematurity	33	21	54	15.97	1	3	16	12	12	2	--	8		
Past maturity	2	2	4	1.18	--	--	--	--	--	--	4	--		
Trauma at birth	54	47	101	29.88	--	1	5	5	8	18	61	3		
Malformation (congenital)	15	22	37	10.94	--	1	8	7	5	5	3	8		
Vaginal bleeding (cause unknown)	2	2	4	1.18	--	--	2	--	--	1	--	1		
Difficult labor (cause not given)	--	2	2	0.59	--	--	--	--	--	1	1	--		
Asphyxia (cause undetermined)	1	--	1	0.29	--	--	--	--	--	1	--	--		
Monnigths (focal)	--	1	1	0.29	--	--	--	--	--	1	--	--		
Fetus papyraceous	--	1	1	0.29	--	--	--	--	--	--	--	1		
Oligohydramnios	1	--	1	0.29	--	--	--	1	--	--	--	--		
Intrauterine death (macerated)	31	23	54	15.97	--	5	2	7	6	9	9	16		
Undetermined	7	6	13	3.84	--	--	--	1	--	2	7	3		

due to the following causes toxemia of pregnancy, placenta previa, abruptio placentae and vaginal bleeding. It is extremely difficult to place these 46 cases in either category, but in all four of them, there is likely to be an inherited factor.

Let us take up these items singly and see in the present state of our knowledge which are likely to respond to preventive measures. First, prematurity. In the analysis of the causes of premature birth it is demonstrated that in a large proportion of cases the cause of the prematurity is unknown. In a certain small proportion syphilis is to blame. This varies in different statistics but nearly every one will agree that in most communities it offers but a small percentage of cases of premature birth and therefore is not a large factor. Syphilis, however, is capable of treatment and presents the most hopeful prospect with which we have to deal in the reduction of fetal and neonatal mortality. Trauma occasionally has been regarded as a factor in prematurity but there seems to be some question as to whether in those cases it is the single factor. Certainly the same trauma does not produce the same results in two individuals. In other words, trauma may be the exciting cause, but there may be also an inherited predisposition to prematurity which results in the birth of the child before term from very slight trauma. Disease in the mother is a factor in production of prematurity. For instance during the epidemic of influenza in 1918, abortion was the rule in women who were pregnant at the time of infection and it is a well known fact that other infections may be the cause of abortion. Not only infections but general diseases such as nephritis, severe heart disease, severe diabetes exophthalmic goiter, etc., may play a rôle. But, even after we have taken into consideration all these causes, it still remains true that the vast majority of cases of prematurity are from causes unknown. In all probability this group represents some defect in the egg and is the result of some aberration in mating, the nature of which, or the natures of which, we do not know. There need be no discussion of the second group that of malformations. These are recognized as a disturbance of inheritance and therefore come definitely within this group. The same may be said of fetal papyraceous oligohydramnios and likewise of intrauterine death (macerated fetus).

When we take up the group which has to deal frankly with the second category syphilis is mentioned first. There is no question but that if syphilitic mothers be properly treated during pregnancy, the majority of infants will be born at term and viable. This group which constitutes about 5 per cent of the cases in Gillespie's table can in large part be saved. The second item, prolapse and compression of the cord is a serious complication of labor as a rule though each may possibly be overcome by obstetrical procedures. The third item, trauma at birth, I shall take up more extensively in the discussion of

TABLE I
CAUSES OF DEATH IN 338 CASES OF STILLBIRTH (GILLESPIE)¹

CAUSE OF DEATH	MALES	FEMALES	TOTAL	PER CENT	AGE, MONTHS							
					LESS THAN 5	5 6	6 7	7 8	8 9	9 10	10 AND MORE	UN KNOWN
Stillbirth	180	158	338	---	1	10	34	42	43	59	101	46
Syphilis	11	7	18	5.32	--	--	1	3	4	7	--	3
Toxemia of pregnancy	6	9	15	4.42	--	--	1	4	3	3	3	1
Placenta previa	4	7	11	3.25	--	--	--	--	3	2	5	1
Abruptio placentae	9	3	12	3.55	--	--	--	2	1	4	4	1
Prolapse and compression of cord	4	5	9	2.66	--	--	1	--	1	3	4	--
Prematurity	33	21	54	15.97	1	3	16	12	12	2	--	8
Past maturity	2	2	4	1.18	--	--	--	--	--	--	4	--
Trauma at birth	54	47	101	29.88	--	1	5	5	8	18	61	3
Malformation (congenital)	15	22	37	10.94	--	1	8	7	5	5	3	8
Vaginal bleeding (cause unknown)	2	2	4	1.18	--	--	2	--	--	1	--	1
Difficult labor (cause not given)	--	2	2	0.59	--	--	--	--	--	1	1	--
Asphyxia (cause undetermined)	1	--	1	0.29	--	--	--	--	--	1	--	--
Moniugitis (focal)	--	1	1	0.29	--	--	--	--	--	1	--	--
Fetus papyraceous	--	1	1	0.29	--	--	--	--	--	--	--	1
Oligohydramnios	1	--	1	0.29	--	--	--	--	--	--	--	--
Intrauterine death (macerated)	31	23	54	15.97	--	5	2	7	6	9	9	16
Undetermined	7	6	13	3.94	--	--	--	1	--	2	7	3

selves as a rule not incompatible with life the congenital defects which affect the vital organs of the body frequently are. Nearly all those conditions affecting the brain such as anencephaly, hydrocephalus, hernia cerebri are fatal in a short time. Congenital brain defects may not be fatal but the condition is such that the individual is as a rule of no value to society. Defects in the gastrointestinal tract are frequently incompatible with life such for instance as esophageal atresia, duodenal atresia congenital absence or atresia of the bile ducts and anal atresia. Some of the minor congenital defects such as Meckel's diverticulum may go undiagnosed causing no symptoms throughout a long life. Congenital defects of the lungs especially congenital atelectasis are often incompatible with life. Some of the other congenital conditions such as congenital cyst of one lung may exist for some time without causing death of the individual. Defects of the heart of a congenital nature are frequently the cause of death at this age but it is surprising how defective a heart may be and the individual still survive. I know of no statistics that will tell us what proportion of cases of congenital heart disease succumb in the first few days of life. The genitourinary defects are rarely incompatible with life at this age. Frequently they will respond to surgical treatment. It is very evident that a large proportion of the congenital defects is necessarily fatal in the first few days of life even if the child be born alive.

As to birth injuries. Those of chief importance are the intracranial injuries which will be taken up later, together with intracranial injuries which cause death of the fetus. The other birth injuries are usually of minor importance or associated with those of the brain. Occasionally rupture of the liver or hemorrhage into the suprarenal capsule may be the cause of death but these conditions are essentially unusual.

For our purpose it is of no special value to go into the question of infections. Certainly infections that occur immediately after birth should be prevented. Occasionally it is difficult to prevent infections, such as meningitis but there is very little excuse for the generalized infections of a septic nature which occur as a result of lack of proper asepsis or antiseptics at the time of birth.

When we come to the question of diseases peculiar to the newborn, an analysis is very enlightening. In almost none of them have we any adequate idea of etiology. Hemorrhagic disease of the newborn from the etiologic standpoint is still an enigma. Those cases of icterus gravis which are not associated with infection are likewise of unknown cause. Idiopathic anemias and generalized edema have so far not been associated with any definite etiologic factor. Winckel's and Buhl's diseases are probably associated with infection. At any rate they are so unusual as to be of little importance in a consideration

of the causes of neonatal deaths. Conditions which cause death in children of later age, such as, bronchopneumonia, nutritional disturbances, etc., are not usual at this time, and may be left out of our calculation. If we look over this list, we find that there is a fair proportion of these children which we can reasonably expect to save even with our present limited knowledge. Even the cases of congenital defects are not hopeless with respect to life. In many instances operative procedures, while extremely hazardous may at times prove life-saving. Those conditions which affect the brain, however, are nearly always fatal or *worse*.

There is very little reason why we should lose any large proportion of newborn infants from infections. It is true that occasionally

TABLE II

CAUSES OF DEATH DURING FIRST FOURTEEN DAYS (HOLT AND BABBITT)²

CAUSE OF DEATH	UNDER 1 DAY		UNDER 7 DAYS		7 TO 14 DAYS		TOTAL IN 14 DAYS		GRAND TOTAL
	PRE MA TURE	FULL TERM	PRE MA TURE	FULL TERM	PRE MA TURE	FULL TERM	PRE MA TURE	FULL TERM	
Congenital Weakness	93	2	120	7	14	2	134	9	143
Accidents of Labor	1	14	1	32	--	--	1	32	33
Pneumonia	--	--	3	9	3	13	6	22	28
Atelectasis	3	7	3	14	1	7	4	21	25
Congenital Syphilis	5	0	6	1	6	0	12	1	13
Malformation	--	4	2	7	0	3	2	10	12
Hemorrhage	--	--	--	8	--	2	--	10	10
Sepsis	--	--	--	2	--	7	--	9	9
Asphyxia	--	7	--	8	--	--	--	8	8
Accidental	--	1	--	2	--	--	--	2	2
Undetermined	--	3	--	8	--	--	--	8	8
Total	102	38	135	98	24	34	159	132	291

a skin infection of the nature of pemphigus neonatorum will be fatal since as yet, we have not learned how to prevent the occurrence of this condition. Taken by and large this group of cases should be eliminated from the list of fatalities of this age.

In regard to the children with diseases peculiar to the newborn, we are in a distinctly bad position. On the other hand, while we do not know the cause of hemorrhagic disease of the newborn, we do know a method of treatment—blood transfusion—which in the vast majority of cases will produce a cure if given at the proper time. Of the children with severe forms of icterus of an infectious nature as yet our knowledge is incomplete. It has been hinted that this condition is due to a disturbance of the hematopoietic organs and that splenectomy may be of value. This remains for future study. The other conditions are rare.

Holt and Babbitt,² Table II, have recorded the cause of death of 291 infants in the first fourteen days of life. If we arrange these ac-

cording to the four groups we find from the accompanying table that in the first group we may include

Congenital weakness	143 cases
Atelectasis	25 cases
Malformations	12 cases

making a total of 180 cases or over 60 per cent of the total. In the second group are those due to trauma. We may include accidents of labor or 33 cases. This leaves 78 in which in 8 the cause was undetermined leaving 70 to be divided between the other two groups. Of these the following may be classed in the group of infections—

Congenital syphilis	13
Sepsis	9
Pneumonia	28

making a total of 50. For the diseases occurring in the first few days of life, the following may be included—

Hemorrhage	10
Asphyxia	8
Accidental deaths	2
	<hr/>
	20

In my experience the figure for pneumonia is quite high but the general statement holds true here as in our estimate.

In the first group it is difficult to see how any could have been saved. Perhaps under ideal circumstances a few of the cases of congenital weakness might have been but when we consider that these children were all born in the hospital we may be sure that every means was used to save them that the most intelligent supervision could devise. It is true that these statistics are somewhat old having been brought out in 1915, but conditions, I am sorry to say, have not materially changed since that time. As to the accidents of labor, or trauma, the figure is very low. Thirty three or less than 10 per cent, is a much lower figure than is given in most reports as the percentage of deaths from injuries.

Adair³ in his statistics of deaths of full term children gives a percentage of 39.7 as due to birth trauma and of those children which were viable at the beginning of labor, a death rate of 41.8 per cent. It should be noted that the statistics of Adair were of general obstetrical practice, largely outside the hospital, and they did not represent obstetrics carried on by experts. Certainly this figure of Holt and Babbitt would represent the absolute minimum of deaths from injury.

As to the third group sepsis pneumonia and congenital syphilis, these should be prevented, and under our present régime the last certainly would be taken care of to a large extent. We would expect to do away entirely with deaths from congenital syphilis with proper prenatal care. The third group represents conditions which are very

TABLE III

	1921	1922	1923	1924	1925	1926	1927	1928	1929	1930	1931	1932	Total
No of Cases	760	745	627	772	753	787	821	827	676	736	971	1489	9964
Deaths—Maternal	1	1	3	3	2	2	2	2	1	1	1	2	21
													0 205%
Cause of Death													
	Card	Pneum	Card	Pneum	Pneum	Card	Pur	Sepsis	Djn.	Ecl	Shock	Resp	
											and	and	
											Col	Col	
											lapse	lapse	
												Item	
Births*	700	745	627	772	753	787	821	827	676	736	986	1501	9991
Stillbirth	17	19	14	29	21	20	19	18	13	14	17	25	226
CAUSES													
Macerated	6	6	3	17	10	11	9	10	6	8	5	9	100
Prematurity	6	4	1	1	3	3	4	3	1	2	1	4	33
Asphyxia	3	8	7	9	8	6	5	5	6	4	6	7	74
Congenital Defects	2	1	3	2	0	0	0	0			4	1	13
Congenital Syphilis							1				1		2
Pulmonary Atelectasis												3	3
Intracranial Hemorrhage												1	1
Neonatal Deaths	15	13	9	14	15	18	15	23	11	8	10	15	166
CAUSES													
Prematurity	3	5	5	5	5	8	9	14	6	5	3	4	72
Asphyxia	3	2		3	3	3	1	6					18
Intracranial Hemorrhage	1	2	1	2	2	3	3	1	1		2	2	20
Hemorrh Dis	2	1	1	2	1	1					2	1	11
Congenital Defects	5	1		2	4	1	2		3	3	1	6	28
Pneumonia	1		1					1				1	4
Sepsis									1				1
Syphilis					3	1		1			2		7
Other Causes		2 ^a	1 ^b			1 ^c						1 ^d	5
													30 %

*Not accurate for 1921 to 1930 inclusive

a. Apnea and nephritis.

b. Edema of larynx

c. Dehydration.

d. Air embolism in coronary artery

hard to deal with. Of these, hemorrhage in the newborn will respond to treatment as a rule, but it is altogether likely that this group of ten cases could not even under ideal conditions be better than halved. Deaths from asphyxia under the conditions of these cases will probably not be reduced. Accidental deaths of course are things which may be guarded against, but in the nature of things there will always be a few and this number of less than 0.5 per cent we can scarcely expect to reduce. If we again sum up the situation so far we find that in Group I of 180 cases, we probably would not be able to save more than 30 at the outside. Group II—33—we could probably not reduce. Group III—50—the figure for sepsis could probably not be reduced, but that for congenital syphilis could be almost entirely erased. Pneumonia might be slightly reduced leaving perhaps thirty cases in this group which we could not expect to save. Group IV—20—we might be able to reduce by five. Of the 291 cases 8 were undetermined leaving a total of 283 to be reckoned with. Thus by our present count under ideal conditions, we could not expect to save more than 55 or about 18 per cent.

I should like at this point to introduce a table (Table III) of the results obtained in the Presbyterian Hospital obstetric out patient department (Chicago) in the years 1921 to 1932 inclusive. This is an out patient department conducted for teaching at Rush Medical College, the labors being attended by students. All normal labors are taken care of in the home, pathologic ones so far as possible are taken to the Presbyterian Hospital. We see from this table that the number of stillbirths exceeded that of neonatal deaths by 60. The outstanding difference between the causes of death in this series and that of Gillespie is that in this series nearly the entire group can be classified as due to inherited causes of one kind or another. Only 2 cases of congenital syphilis and one of intracranial hemorrhage out of 226 would not fall in this category. I might say that practically all of these diagnoses were made at autopsy so that there was very little guess work as to the cause of death. As to the neonatal deaths they conform very closely to those of Holt and Babbitt, so that we will not discuss these further at this time.

Let us now consider the question of intracranial hemorrhage as a cause of death at this period of existence. If we compare the statistics of Holt and Babbitt with those of Adair, we find in the former that in full term children accidents of labor account for 32 or approximately 10 per cent (Presbyterian Hospital 20 or 12 per cent), while in the statistics of Adair the figure is 31 per cent. This difference of 21 per cent is a very great difference. Three times as many infants born under the conditions which were represented in Adair's report died as compared with the infants born in the Sloane Maternity Hospital of New York City and the Presbyterian out patient service in

Chicago To evaluate this discrepancy is very hard At first glance, it would seem that this difference was due to a difference in the type of obstetrics employed in the two situations On the other hand, while we must admit that there is probably some reason for this conclusion, or rather that it in part accounts for the difference, we must remember that there is a vast amount of racial difference between the populations of New York and Chicago and the population of Minnesota Whether or not this plays a part in these statistics, it is impossible to say, but there can be very little doubt but that good obstetrics did play a part

It is impossible to tell from the statistics of Gillespie what proportion of the deaths from birth trauma was the result of interference with birth, and how much was the result of the natural processes of labor For the consideration of our subject, this is the important point If the processes of labor are responsible for intracranial hemorrhage of the newborn (which accounts for the vast majority of fatal birth trauma), then our efforts to reduce the mortality from this cause are likely to be largely futile If, on the other hand, the cause of intracranial hemorrhage is to be carried back in the majority of instances to obstetric interference, it will be possible for us to attack this problem with some prospect of success

A more careful analysis of the causes of fetal deaths brings out the fact that most of them are to be accounted for on the basis of prematurity and that a large proportion of these cases born in the normal process of labor cannot be attributed to interference by the physician It is also true that in full-term infants born by Cesarean section or precipitate labor it is not unusual to have intracranial hemorrhage, and even in the normal process of labor, children with large heads may occasionally be victims of the same condition It has been my impression in the study of this subject that while we may be able to reduce this group materially by less interference at the time of labor, there still would be a very large proportion of cases where this will not be possible Among these may be grouped the cases of intracranial hemorrhage which occur in spontaneous labors, Cesarean sections, and precipitate labors Again we must expect that if we delay the interference too long in many cases there is likely to be hemorrhage simply from the exaggerated efforts of the uterine musculature Like so many things in medicine, the ultimate result depends not upon dogmatic rules but upon judgment, and we cannot expect to have perfect judgment exercised in every case of labor If we are able, therefore, to reduce the number of cases of intracranial hemorrhage in the newborn by one-third, it would seem to me that that would be as much as we could expect

SUMMARY

When we sum up this estimate as to the prospects of saving the newly born infant and the child not yet born, we find that the prospects are not so bright as we could wish. Statistics of other countries are misleading because of different methods of compilation, and we are only interested in them in an academic way. What we wish to know is what chances have we of reducing this mortality under present and future conditions. Under present conditions our chief hope lies in the reduction of the cases of deaths from congenital syphilis reduction of cases of sepsis and of birth trauma. The large group of cases of malformation congenital debility and allied conditions offer very little hope. We must not be carried away with enthusiasm to the point where we may expect a result comparable to that which has been brought about in the reduction of infant mortality in general. This is the most remarkable life saving activity that has taken place at any time since the introduction of smallpox vaccination. The problem was much more clear and the chances of success much greater when this effort was started than is true at the present time with respect to the fetus and the newly born. But the position is not quite so dark as these statements would seem to indicate. Medical science is advancing rapidly and we as yet have accomplished little or nothing in the study of these conditions. A closer study may develop some very unexpected leads. It is not impossible that we may find that nutrition does play a part in congenital debility. We may be able to grasp the causes of some of the fatal conditions in the newly born infant and it may be that with a better understanding of eugenics we will be able to prevent some of the congenital malformations and conditions which at the present time have proved so fatal. This program, however, is not a program of months but of years and probably of decades, and those who interest themselves in this life saving venture must realize the problems ahead of them and the chances for success.

REFERENCES

- 1 Gillespie. Am J Dis Child. 44 9 1032
- 2 Holt and Babbitt. J A M A 64 287 1923
- 3 Adair. J Mich. State M S. 31 363 1932.

RENAL CHANGES IN THE RABBIT RESULTING FROM INTRA- VENOUS INJECTION OF HYPERTONIC SOLUTION OF SUCROSE

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IN A SERIES of experiments on rabbits in which hypertonic solution of sucrose was used to produce maximal diuresis, marked cytologic changes were observed in the convoluted tubules of animals that were killed twenty-four hours after injection. It seemed worth while to determine the mode of development of these cytologic changes, and to attempt to correlate them with the possible functional changes of the kidneys. If, in spite of the histologic changes, the functional changes were minimal, the diuretic action of intravenously injected sucrose might prove safe as well as useful therapeutically.

Various observers² have recorded changes in the epithelium after injection of hypertonic solutions of sugar. But more detailed studies of the histologic changes, or the effects of repeated injections on the renal epithelium have not been given.

DEVELOPMENT OF LESIONS AFTER A SINGLE INJECTION

Animals were given injections of large amount of 20 per cent sucrose for one hour. After intervals varying from one hour to fifteen days (one, three, six, twelve, twenty-four, forty-eight, ninety-six, one hundred twenty, one hundred sixty-eight, two hundred forty and three hundred sixty hours) the animals were killed and the changes in the renal structure noted (Table I).

The swelling of the convoluted tubules began after one hour and reached its maximum at forty-eight hours, so that not only the cells, but the tubules themselves seemed larger than normal. This enlargement of the cells persisted for about a week and then gradually subsided, so that at the end of fifteen days the cells appeared normal. In the early stages, the vacuolar degeneration was marked, it was of maximal intensity in the tubules of the ascending limb of the loop of Henle. In some sections a definite zone in the cortex adjacent to the medulla was formed by this change in the epithelium. After one hour the tufted edge of the epithelium was still present, but it was absent after three hours. After twenty-four hours, the protoplasm became finely granular and small in amount, so that the cells came to stain lightly, and after forty-eight hours, the appearance of the cells was that of clear cells of hypernephroma. After twenty-four to forty

eight hours, the cells of the tubules were so swollen that the lumen was almost obliterated (Fig 1). When a lumen was present it was filled with finely granular material which stained pink in sections prepared with hematoxylin and eosin. After one hour the nuclei were round or oval, after three hours they appeared shrunken, and in five of six specimens obtained in the first forty eight hours the nuclei of the tubule cells were definitely shrunken, and cellular outlines were rather indistinct. This nuclear change was not noted after the second day. After the seventh day the swelling of the tubular epithelium began to subside. Ten days after injection, some enlargement of the tubular epithelial cells was still present and the protoplasm was still finely granular and faintly staining. In specimens obtained at the



Fig. 1.—Vascular degeneration and swelling after twenty four hours.

fifteenth day the kidney was normal. When smaller doses of sucrose were given, the tubules were practically normal after one week.

In specimens obtained at one, three and six hours, there was no material within Bowman's capsule. In these early stages an excess number of eosinophilic leucocytes in the glomerular capillaries were seen; these were absent later. The glomerular tufts did not fill the capsule. After twelve hours there was less space between tuft and capsule, and in many cases, the space was filled with eosin staining granular material. The specimens obtained at twenty four and forty-eight hours resembled those obtained at twelve hours. After ninety-six hours, the glomeruli appeared normal.

It should be noted that the diuresis which reached its maximum in the case of an animal that excreted 150 cc for each kilogram of body

weight each hour, was sufficiently great to produce a moderate degree of hydronephrosis. The hydronephrosis was seen in animals killed immediately after injection.

The changes produced by injection of 50 per cent solution of sucrose resembled closely those produced by 20 per cent solution, except that at the one- and three-hour stages, the epithelium seemed lower than normal, retained its tufted edge, and the vacuolar degeneration was less.

Injection of 10 per cent sucrose produced decidedly less renal injury in the convoluted tubules, the ascending limb of the loop of Henle seemed most involved, but at no stage was tubular swelling so intense, nor was the lumen at any stage completely obliterated.

TABLE I

RENAL CHANGES AT VARYING INTERVALS AFTER INTRAVENOUS INJECTION OF SOLUTION OF SUCROSE

RABBIT	HOURS AFTER IN- JECTION	URINE, C C PER KG PER HOUR	SWELLING OF TUBULAR EPITHE- LIUM	VACUOLAR DEGEN- ERATION	DETRITUS IN LUMEN	GRANULAR DETRITUS IN GLOMERULAR SPACE	SHRUNK EN- NUCLEI
1	1	190	+	++	++	-	-
2	3	185	+	++	++	-	++
3	6	23	+++	+++	++	+	+
4	12	143	+++	+++	+	+	-
5	24	83	++++	++++	+	++	-
6	48	60	++++	++++	-	++	-
7	96	93	+++	++	+	-	++
8	120	40	+++	++	-	+	+++
9	168	153	+++	++	-	-	-
10	240	75	++	+	-	-	-
11	360	117	+	+	-	-	-

DEVELOPMENT OF LESIONS AFTER REPEATED INJECTIONS

Series 1—It was evident that single injections of sucrose would be tolerated by the rabbit's kidney without permanent injury, and that the appearance of the tissues would return to normal in from seven to fourteen days. It seemed advisable, therefore, to determine whether repeated injections, at intervals less than those necessary for complete repair, would injure the convoluted tubules and affect the functional capacities of the kidney. The first eighteen animals were given injections at intervals of from five to seven days and were given from three to eight injections. The amount of 20 per cent solution of sucrose injected varied from 542 c c given in eight injections to a rabbit weighing 1.5 kg to 1,480 c c given in four injections to a rabbit weighing 3.6 kg. The younger rabbits did not tolerate the injections as well as the older animals. In the kidneys of animals killed within five days after the last injection, there were only the typical changes described as following the single injections in forty-eight hours, but the changes varied considerably in their intensity.

Series 2—Nothing of note was observed in the first series of animals. Therefore, it was decided to increase the number of injections, and a second series of animals received from ten to twenty two injections at intervals averaging about seven days. In Table II the details of weight, number of injections, total amount of 20 per cent solution of sucrose, intervals between injections, interval between last injection and death of animal and the histologic findings are given. It was clearly evident that even after numerous injections the epithelium displayed a remarkable power to return to normal. This was most evident in animals 1 and 2 which died eight days after the twelfth and tenth injections, respectively, and in the kidneys of which there were practically no histologic changes. This recuperative power was exhibited to a slightly less degree in animal 6 which died eleven days after its fourteenth injection, and in which there were only slight changes in the renal tubules. In rabbits 5, 9 and 10, which died two or three days after the last injection, the changes in the convoluted tubules were striking. The cortex of the kidney resembled hyponephroma with compressed glomeruli. With the exception of rabbits 6 and 7, rabbit 9 received the largest amount of sucrose 1800 cc in sixteen injections, but there were no changes that in any way differed from those found in a rabbit that had been killed forty-eight hours after a single large injection. In its sixteenth injection it received 150 cc of 20 per cent solution of sucrose in fifty minutes and during that time put out 200 cc of urine. Ten days before its death and forty-eight hours after the fourteenth injection, the output of phenolsulphonphthalein was 60 per cent.

Rabbit 4 was of interest on account of rather peculiar changes seen at necropsy, after only fifteen injections. The entire convoluted tubule took an excessive amount of stain, and although the animal died on the day of injection, the cells of the tubules were not typically swollen. The nuclei were dense and deeply stained. The picture was different from that seen in any of the other animals. In the three animals which received sixteen, twenty one, and twenty two injections, such changes were not seen, therefore the picture presented probably was not the result of repeated injection of sucrose.

Rabbits 8 and 9 received fourteen and sixteen injections, respectively, and the changes varied with the interval of time after the last injection. The changes were mild in animal 8 which died eleven days after the final injection and marked in animal 9 which died three days after the final injection.

Rabbits 6 and 7 received the largest number of injections, rabbit 6 received 3025 cc in twenty-one injections and rabbit 7 2555 cc in twenty two injections. In order to show the amount of sucrose injected the figures are given in Table III. There also are given the time of removal of the right kidney and of determinations of blood urea.

TABLE II
RENAL CHANGES AFTER REPEATED INJECTION OF 20 PER CENT SOLUTION OF SUCROSE

RABBIT	WEIGHT, KG	INJECTIONS OF SOLUTION OF SUCROSE	SOLUTION OF SUCROSE INJECTED, TOTAL CC	DAYS BETWEEN LAST INJECTION OF SUCROSE AND DEATH	TUBULAR CHANGES						SCLE- ROSIS	COMMENT
					SWELLING		DEGEN- ERATION	ATROPHY	META- PLASIA			
					ASCENDING LOOP OF HENSEL	CONVOLUTED						
1	25	12	1,542	8	++	0	0	0	0	0	After 12 injections, blood urea 22 mg in each 100 cc, excretion of phenol sulphophthalein, 75 per cent	
2	16	10	720	8	0	0	0	0	0	0	After 10 injections blood urea 8 mg in each 100 cc, excretion of phenolsulphophthalein, 75 per cent, vacuolar degeneration one, liver cells +++	
3	24	10	965	6	+++	+++	0	0	0	0	Specimen removed for control before injection, negative	
4	275	15	1,036	0	0	0	++	+	+++	++		
5	271	13	1,271	2	+++	+++	0	0	0	+	Specimen removed for control before injection, negative	
6	34	21	3,025	1	++	+++	+++	++	0	+	Specimen removed for control, negative, blood urea 116 mg in each 100 cc, excretion of phenolsulphophthalein, 5 per cent	
7	32	22	2,555	2	+++	+++	+++	+++	0	++	Marked compression, atrophy of ascending limb of loop	
8	20	14	1,482	11	+	+	++	+	0	0		
9	25	16	1,800	3	+++	+++	+++	0	0	0		
10	275	11	1,161	3	+++	+++	+++	+	0	0		

and of excretion of phenolsulphonphthalein. After nine and ten injections the output of phenolsulphonphthalein was 80 and 70 per cent. A week after right nephrectomy, and following the thirteenth injection in rabbit 6, and the sixteenth injection in rabbit 7 the output of phenolsulphonphthalein was respectively 60 and 55 per cent. At no time after removal of one kidney did the animals excrete a volume of urine greater than the volume of sucrose injected. The general condition of the animals became poor and they lost weight.

Animal 6 weighed 3.1 kg. at the beginning of the injections. One hundred eighty-two days later, twenty-four hours before it died, it weighed only 2.1 kg. At the time of the last injection it seemed very weak and put out only 10 cc. of urine while 85 cc. of sucrose was injected. The day following this injection the value for blood urea was 116 mg. for each 100 cc., and the output of phenolsulphonphthalein was only 5 per cent in two hours. The animal was so sick that it was feared it would not live another day, therefore it was killed. Postmortem examination disclosed that the animal was markedly emaciated. The left kidney was practically normal in appearance in spite of the fact that a piece of it had been removed after the tenth injection. Removal of the specimen had resulted, of course, in a small scar. The kidney was slightly increased in size, and was light brown. The surface was slightly irregular. The ureter and bladder were normal. Examination of the other organs disclosed nothing abnormal. Three specimens were available for microscopic studies. The first was derived from the piece of the left kidney that had been removed six days after the tenth injection. The vacuolar degeneration of the cells of the ascending limb of the loop of Henle was marked, as was also that of cells from some parts of the convoluted tubules. Some of the convoluted tubules had undergone little change, in others the cells appeared markedly swollen and the outlines of the cells were indistinct. Some focal nephritis was present. The second section, removed from the right kidney, six days after the thirteenth injection, differed very little from the first section. The degeneration and swelling of the cells of the ascending limbs of the loops of Henle were more marked than of the cells of the convoluted tubules, however, were, if anything, a little less marked and many tubules appeared normal. Some focal nephritis was present. In the third section taken at necropsy from the left kidney after twenty-one injections there was much more focal nephritis than there was in the other two sections. The protoplasm of the cells of the convoluted tubules was finely granular and the cells were swollen so as to occlude the lumens of a few of the tubules. Most of the cells of the tubules were swollen relatively little. The cells of the ascending limb of the loop of Henle contained even less protoplasm, in some places the cells were greatly swollen but in others they were atrophic. The structure of the kidney otherwise was normal, and the changes, other

than the focal nephritis, were not nearly so intense as in the kidneys of many of the other animals which received fewer injections. Malloy-Heidenhain stain did not disclose any diffuse increase of connec-

TABLE III

RESULTS IN EXPERIMENTS IN WHICH LARGEST NUMBER OF INJECTIONS OF SOLUTION OF SUCROSE WAS GIVEN

INJECTION OF SOLUTION OF SUCROSE	SOLUTION OF SU CROSE, C C		COMMENT
	RABBIT 6*	RABBIT 7†	
1	180	125	
2	200	115	
3	50	115	
4	100	150	
5	200	100	
6	200	150	
7	100	150	
8	150	100	
9	45	165	Rabbit 6 after ninth injection excretion of phenolsulphonphthalein 80 per cent
10	150	150	Rabbit 6 small piece left kidney removed Rabbit 7 after tenth injection, excretion of phenolsulphonphthalein 70 per cent
11	95	50	
12	150	200	
13	200	25	Rabbit 6 right kidney removed 133 days after first injection, 7 days later blood urea 24 mg in each 100 c c and excretion of phenolsulphonphthalein 60 per cent
14	200	40	
15	150	50	
16	50	200	Rabbit 7 right kidney removed 138 days after first injection, 7 days later blood urea 27 mg in each 100 c c. and excretion of phenol sulphonphthalein 65 per cent
17	200	175	
18	200	100	
19	40	45	
20	180	200	
21	85	100	Rabbit 6 on day after twenty first injection, blood urea 116 mg and excretion of phenol sulphonphthalein 5 per cent, animal very weak so killed 182 days after first injection
22		50	Rabbit 7 second day after twenty second injection found dead, 176 days after first injection (animal pregnant)
Total	2,925	2,555	

*Rabbit 6 weight 3.4 kg Urine negative on culture and microscopically

†Rabbit 7 weight 3.2 kg Urine negative on culture and microscopically blood urea 7.5 mg in each 100 c c and excretion of phenolsulphonphthalein 100 per cent.

tive tissue. Microscopic changes that would account for the high value for urea, and for the final low value for excretion of phenol-sulphonphthalein were not found.

Animal 7 died twenty-four hours after the twenty-second injection. It appeared to be in good condition following the last injection of 50 c c of sucrose, but was found dead the following morning, one hundred seventy-six days after the first injection. There was considerable

postmortem change. The right kidney was definitely enlarged and the tissue was opaque and grayish. On section, the cortex was definitely increased in width. The pelvis and urator were normal. The other abdominal organs were normal. There were available for histologic study, sections from the left kidney, that had been removed after sixteen injections, and sections from the right kidney, made at necropsy. The sections from the left kidney disclosed relatively little change. The cells of the ascending limb of the loop of Henle and those of the convoluted tubules, disclosed some vacuolar degeneration but relatively little swelling. The interval of six days seemed to have been sufficient to allow the cells to return to normal size. There was some chronic focal nephritis. The section taken at necropsy, twenty



Fig 2—Epithelial atrophy and sclerosis after twenty-two injections.

four hours after the twenty second injection, disclosed marked changes that in part might have taken place postmortem. There was marked degeneration and swelling of the tubules and the cells especially those of the ascending limbs of the loops of Henle, appeared crowded together as if undergoing atrophy (Fig 2). The line between the cortex and medulla was difficult to discern. There was considerable diffuse increase in connective tissue especially in the lower portion of the cortex and upper part of the medulla. Sections stained with Mallory Heidenhain stain disclosed the increase in connective tissue definitely this was especially evident when compared with a section from rabbit 6 stained in the same way, in which no such increase in connective tissue was seen. It is to be regretted that this animal was not found immediately after death, for it is the one animal in which

atrophy of the tubules and diffuse increase in connective tissue occurred. It does not seem likely that postmortem changes can account for this difference, for the cellular outlines were well preserved. These changes, which were absent in rabbit 6, may represent the more severe tubular changes that follow injection continued over even longer periods.

Series 3—A third group of seven animals received a smaller number of injections of solution of sucrose, but at shorter intervals. Animals 1 and 2 received their injections at intervals of two days, the former received six injections, and the latter, eight. The other five animals received four injections, at intervals of three days. In all the animals in which tissue was available for histologic study the renal

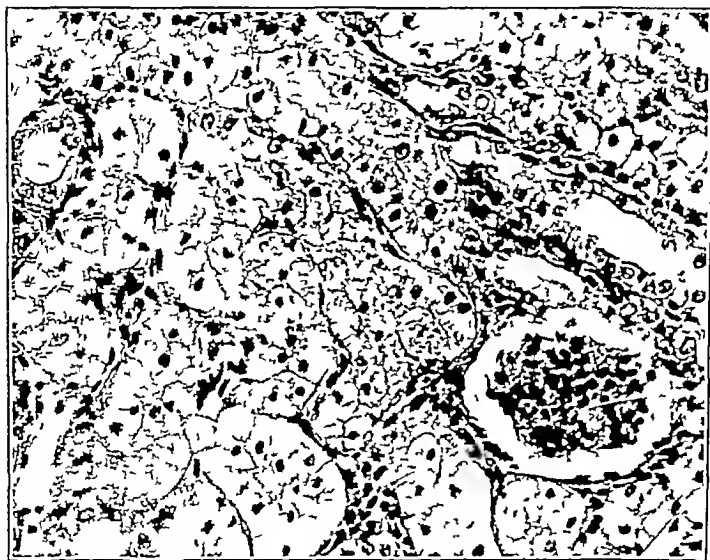


Fig 3—Tubular degeneration after eight injections at two-day intervals

changes were marked, except in animal 6 which was not killed until eight days after the fourth injection. The kidneys of all but the first two animals had been removed one week before the first injection. The changes found in this series of experiments were the most uniformly marked, and represented the changes resulting from injury that was repeated before the process of healing could return the cell to normal. Fig 3, picturing tissue of animal 2 after eight injections at intervals of two days, presents the most marked acute lesion that I have encountered. The swelling of the tubular epithelium was most marked and the lumen of most of the tubules was closed. Fig 4 illustrates the changes after four injections at intervals of three days. It represents changes almost as intense, and some calcareous deposits probably not related to the injections.

The most striking feature of this series of experiments, aside from the changes seen, was the marked reduction in output of phenolsulphophthalein in the five experiments in which determinations were made. In two of the experiments the urine was taken for only two hours after injection of the phenolsulphophthalein in the other three for four hours (Table IV). The output in the five experiments was extremely low. 5 per cent in three cases, 3 per cent in one case, and zero in the fifth case. The output of phenolsulphophthalein by animal 6 had risen to 15 per cent on the seventh day after the last injection, by animal 7 it was 20 per cent seven days after the last injection, and 80 per cent thirteen days after the last injection.



FIG. 4—Tubular degeneration after four injections at three-day intervals.

The typical picture twenty four to forty-eight hours after a large injection of 20 per cent solution of sucrose was that of hypernephroma. The entire system of tubules of the cortex lost the solid pink color as seen in a section stained with hematoxylin and eosin and consisted of clear cells, with a small amount of pink granular material. The cells were so swollen that there appeared to be only a very narrow lumen or no lumen. After six to fifteen days, depending on the dose, the epithelium again appeared normal. A second injection would produce the same histologic appearance, and if continued for as many as twenty two injections, provided the interval of time was seven days or more, resultant changes would not affect the excretory functions of the kidney. If the interval of time was only three days, definite functional changes resulted, as measured by the output of phenolsulphophthalein.

TABLE IV

RESULTS IN EXPERIMENTS IN WHICH A RELATIVELY SMALL NUMBER OF INJECTIONS OF SOLUTION OF SUCROSE WAS GIVEN, BUT AT RELATIVELY SHORT INTERVALS

RABBIT	WEIGHT, KG	DATE OF IN- JECTION OF SOLUTION OF SU- CROSE, MG	SOLUTION OF SUCROSE, G/G	INTERVAL BE- TWEEN INJE- TION OF SUCROSE AND OF PHENOL SULPHON PHTHALEIN*	OUTPUT OF PHENOL- SULPHON PHTHAL- FIN, PER CENT	SWELLING OF TUBULES	VACUOLAR DEGEN- ERATION	DAYS BE- TWEEN LAST INJECTION OF SOLUTION OF SUCROSE AND DEATH	COMMENT
1	2.55	11 7 11 9 11 13 11 15 11 17 11 19	80 100 104 105 82 100						
2	2.5	11 7 11 9 11 13 11 15 11 17 11 19 11 21 11 23	100 85 103 100 100 100 70 93			+++	++	2	Pycitis, shrunken nuclei
3†	3.5	1 20 1 23 1 27 1 30	100 83 100 100	5 hours 1 day	3† 5	+++++	++	3 6	Postmortem change marked

TABLE IV—Cont'd

RABBIT	WEIGHT KG	DATE OF IN- JECTION OF SOLUTION OF SU- CROSE, MG.	SOLUTION OF SU- CROSE, C.C.	INTERVAL BE- TWEEN IN- JECTION OF SU- CROSE AND INJECTION OF PHENOL- SULPHON PHTHALEIN	OUTPUT OF PHENOL- SULPHON PHTHALEIN IN PER CENT	SWELLING OF TUBULES	VACUOLAR DEGEN- ERATION	DAYS BE- TWEEN LAST INJECTION OF SOLUTION OF SU- CROSE AND DEATH	COMMENT
4†	2.75	12.31 1 3 1 6 1 9	100 105 130 53						Died at end of experiment
5†	2.9	12.31 1 7 1 6 1 9	150 70 100 100			+++	+++	0	Deposit of calcium in tubules
6†	2.11	1.30 1.03 1.31 1.30	100 35 131 100	1 day	5†	++++	++	5	Output of phenolsulphophthalein seventh day 13 per cent chronic nephritis
7†	2.73	1.22 1.27 1.28 1.30	100 100 100 50	1 day	0		+++	3	Output of phenolsulphophthalein seventh day 20 per cent thir- teenth day 80 per cent no sec- tions; animal lived

Phenolsulphophthalein, 1/2 ampule, given in 50 c.c. Ringer's solution intravenously urine collected for 4 hours

†Urine collected for 1 hour.

‡Left kidney removed 1 week before injections of solution of sucrose were begun.

CHANGES IN THE KIDNEYS OF HUMAN BEINGS

Changes similar to those described occurred in the kidneys of human beings after injections of hypertonic solution of sucrose. If, as a result of repeated injections of solution of sucrose for the purpose of inducing diuresis, permanent injury would result, a contraindication to use of this solution as a diuretic would be evident. Fig 5 illustrates the condition of the kidney of the human being forty-eight hours after a series of injections of solution of sucrose.

The course of the illness was as follows. A boy aged eight years was brought to the clinic. When he was three months of age, a diagnosis of congenital syphilis was made and treatment had been continued since that time. The illness for which treatment was sought

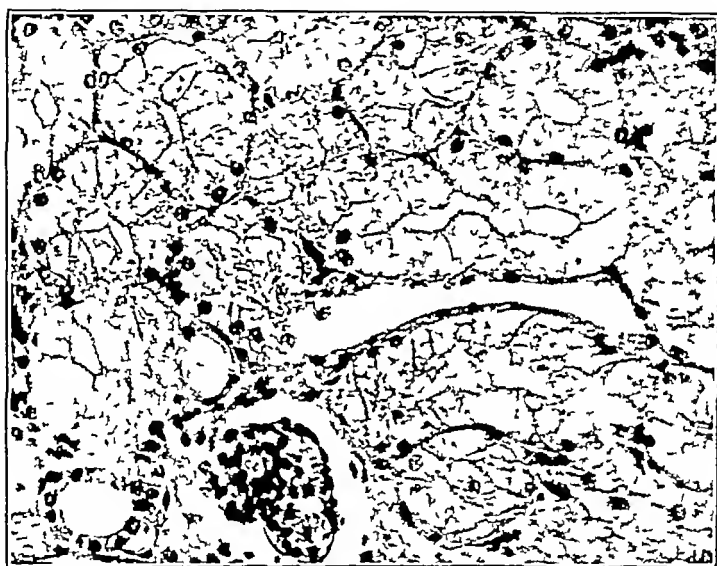


Fig 5—Kidney of a patient after three injections

at the clinic was meningitis. The spinal fluid contained diplopneumococci, type 4, on culture. The boy's condition rapidly became worse, high fever developed, and death occurred on the fifth day after his admission. On the second day after admission he was given 1,000 c c of 20 per cent solution of glucose intravenously, on the third day, he was given 450 c c, and on the fourth day, 790 c c. This was administered after sodium amytal had been given hypodermically.

At necropsy there was evidence of acute meningitis and of congenital syphilis. The epithelium of the ascending limb of the loop of Henle, and of the convoluted tubules, was swollen and pale, the cells were represented by a thin membrane, and a very pale, faded cytoplasm. The swelling of the epithelial cells was so marked as completely to obliterate the lumen of the tubules. There was considerable pink granular material within Bowman's capsule.

COMMENT

As the result of the experiments in series 3, it seemed evident that injections at intervals of three days seriously lowered the function of the renal epithelium as measured by the output of phenolsulphonphthalein. Intervals of three days between injections it seemed were insufficient to permit return of function of the renal tubules.

The changes produced in the epithelium of the ascending limb of the loop Henle and convoluted tubules were striking, and so different from those provisionally described for the tubular system, that some speculation as to mode of origin of these changes seems justified.

Marshall has shown that the aglomerular fishes do not secrete foreign sugar, therefore, it would seem probable that sucrose is excreted by the glomeruli, and that it is passed from there through the tubular system into the renal pelvis. The epithelium which normally concentrates the urinary constituents by the absorption of water is, in all probability, doing the same thing during diuresis induced by sucrose. The tremendous outpouring of urine, which may reach 150 cc for each kilogram of body weight, each hour, involves a huge functional load on the kidney, which is manifested only by the tubular changes. Apparently the glomerulus is in no way injured by putting out this large amount of urine, even though repeated injections are made at a time when the renal tubules are swollen. The changes in the convoluted tubules can be thought of as a physiologic response to a maximal effort in retaining water for the body or perhaps, as a response to a physical injury from overwork. The return of normal in a relatively short time indicates the absence of severe, irreparable injury. The lesions resembled those Hartman produced in the kidney when he transplanted the lower ends of the ureter high into the duodenum and thus established a closed circuit for excretory waste products.

SUMMARY AND CONCLUSIONS

It is evident from these experiments that repeated injections of hypertonic solutions of sucrose do not do any harm to the tubular apparatus or glomeruli of the kidney unless injections are given repeatedly at short intervals.

Four injections of hypertonic solutions of sucrose at intervals of three days reduce the output of phenolsulphonphthalein materially with a return to normal output after two weeks.

It may be concluded that intravenous injections of hypertonic solutions of sucrose, for the purpose of diuresis or of dehydration, given singly or repeated after intervals of five to seven days, will not prove harmful.

REFERENCES

- 1 Hartman, F. W. Personal communication to the author.
- 2 Lamy, Henry, Mayer, André, and Rathery, F. *Journal de physiologie et de pathologie générale* 8: 624, 1906.
- 3 Marshall, E. K., Jr. *Am. J. Physiol.* 84: 1, 1930.

FAMILIAL RETARDATION IN OSSIFICATION OF THE CARPAL CENTERS

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THE instance of familial retardation in the development of carpal centers to which we wish to call attention is interesting in itself from several points of view, but has greater significance in connection with the rôle of constitutional and of local factors in the ossification of cartilage. The case involved two brothers whose clinical course we were able to follow, year by year, for a period of over five years and until the defect in ossification was completely corrected. During this observational period it was possible to make careful measurements of the various parts of the body, to carry out chemical examinations of the blood and to observe the physical and mental progress of the boys.

CASE 1—L. Y. (older brother), a Jewish boy, was born at full term, February 21, 1921. His mother, an Austrian, twenty-nine years of age, physically normal, had been married two years before he was born. There had been no miscarriages. About two years later she had another child whose history is given below. A third pregnancy terminated, however, at the eighth month, when she gave birth to an anencephalic monster weighing 2 pounds, 7 ounces. The father, also of Austrian extraction, was about 37 years of age and physically sound. There was no history of familial disease.

Throughout the first pregnancy the mother enjoyed fair health, her diet apparently was adequate. The delivery was normal, the respirations of the infant spontaneous and there were no convulsions. Birth weight was 7 pounds, 4 ounces. The infant was breast fed until about 14 months of age. During this period attempts were made to add other articles of food to the diet, but without suc-

TABLE I
DATA IN REGARD TO DEVELOPMENT OF THE OLDER BROTHER (L.)

FIGURE	DATE	AGE (YEARS)	WEIGHT (POUNDS)	HEIGHT (INCHES)	COMPARISON WITH BALDWIN WOOD STANDARDS	NUMBER OF CARPAL CENTERS	
						LOUIS	PRYOR'S STANDARD (MALE)
—	3/15/27	6	42¼	44	per cent -4	2	6 - 7
2 a	12/ 5/27	6¾	—	—	—	2	6 - 7
—	5/ 5/28	7¼	49¾	46½	+1	2	6 - 7
2 b	1/13/29	8	49½ ¹¹ / ₁₆	49½	-11	2*	6 - 7
2 c	11/25/29	8¾	55¼ ¹¹ / ₁₆	49¾	-2	5 & 6	7
—	10/12/31	11	63	53	-6	—	8

Right ulna distal epiphysis appears 2 years retarded

cess. Cod liver oil was never given. After the fourteenth month thin cereals zwieback, broth and potatoes were taken by the child who still refused fresh fruits and meat. Motor development was retarded. The infant was able to support its head at 6 months of age and sat up at 9 months. He never crawled and was able to walk with support only at 17 months and walked alone by about 18 months. Talking also was delayed, single words being spoken at 18 months and he was unable to put two or more words into a phrase until 2 years of age. The first tooth erupted at 10 months.

Up to about 6 years of age, the child had had no illnesses of importance. Tonsillectomy and adenoidectomy were performed at 2½ years. At 6 years, however, he was admitted to a hospital for acute mastoiditis which became complicated by an acute suppurative arthritis of the right knee joint. The knee was incised and drained, leading to ankylosis of the joint. The clinical course of the disease was stormy and convalescence protracted.



FIG. 1.—L. Y., eight years nine months, and G. Y., seven years.

Upon recovery, physical examination showed a poorly nourished boy weighing 42 pounds, 4 ounces, with a height of 44 inches. The circumference of his head was 18½ inches, that of his chest 22 and of his abdomen 19½ inches. The mid point of the body was at the symphysis pubis. His general expression was dull and his color poor. He was a mouth breather. The musculature was flabby and the subcutaneous fat deficient. The posture was poor due to the deformity of the right lower extremity. The spine showed a compensatory scoliosis to the right, the weight of the body being shifted to the left. There was a partial ankylosis of the right knee joint with beginning atrophy of the muscles.

The skin was clear and covered with a normal growth of lanugo hair. The hair of the scalp was abundant coarse and dark brown and the eyebrows and eyelashes were normal. The palpebral fissures were equal and the pupils reacted promptly to light and accommodation. The ears, lips, mouth and tongue were normal. The deciduous teeth showed caries of the two upper middle incisors, as

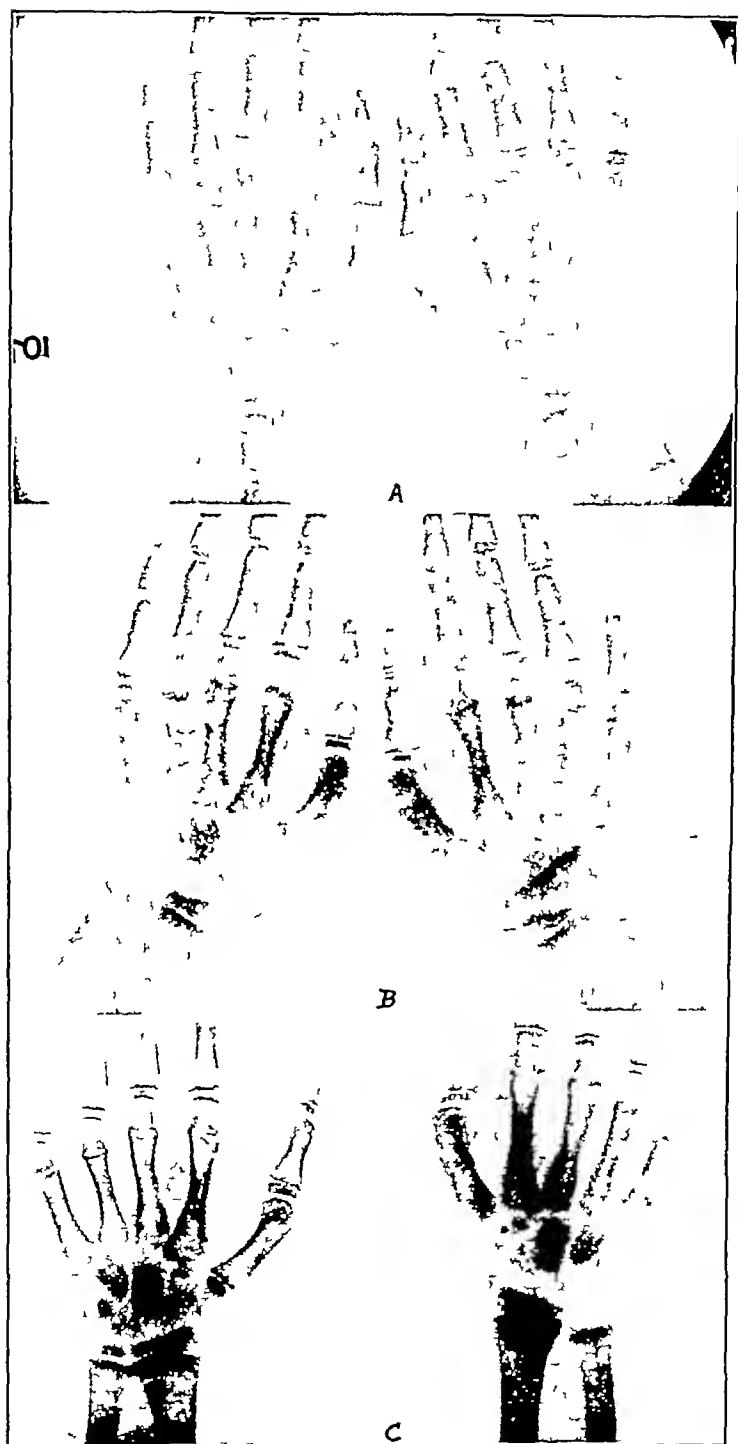


Fig 2—L. Y (older brother)

(a)—Carpal centers at 6 $\frac{3}{4}$ years

(b)—Carpal centers at 8 years

(c)—Carpal centers at 8 $\frac{1}{4}$ years

Note sudden accession in the course of less than a year

well as of the right lower anterior molar. It may be added that subsequent examination of the teeth, when the boy was eleven years of age revealed caries of two of the four permanent first molars and of all the deciduous molars. The chest was symmetrical and the heart and lungs normal. The abdomen revealed

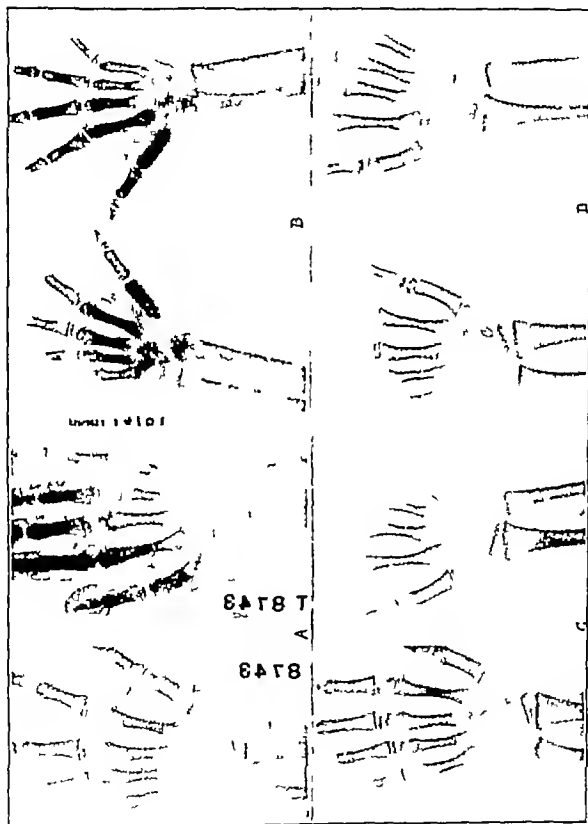


FIG. 3.—C (younger brother)
(a)—Carpal centers at 5 years
(b)—Carpal centers at 6 1/2 years
(c)—Carpal centers at 7 years

nothing unusual. The genitals appeared to be underdeveloped but the testicles were fully descended. With the exception of the right lower extremity the limbs were normal. The nails of the fingers and toes were dull in lustre but showed no fissures or furrows. The deep reflexes of the normal extremities were active. Mentally the boy appeared to be of average ability.

During the course of observation, roentgenograms were taken of the various

bones and joints of the body To our surprise, it was found that films showed only two centers of calcification of the carpal bones, despite the fact that the boy was over six years of age (Fig 2 A) This indicated a marked retardation in development of these centers, as, normally, at this age 6 to 7 centers should have been evident All the metacarpal and phalangeal epiphyses were present Roentgenograms of the tarsal bones of both ankles revealed 6 and 7 centers, which corresponds to the norm for this age

CASE 2—(younger brother)—G Y In view of the retardation in development of the carpal centers of L it was thought advisable to take roentgenograms of the wrists of the younger brother, who at this time was 4 years and 4 months of age Films showed a similar retardation in the process of calcification in that only two centers and the beginning of a third, were to be seen in either wrist (Fig 3 A) According to the standards of Pryor,⁴ a boy of this age should have 4 or more carpal centers showing calcification The metacarpal and phalangeal epiphyses were present Roentgenograms of the tarsal bones showed normal calcification

TABLE II
DATA IN REGARD TO DEVELOPMENT OF THE YOUNGER BROTHER (G)

FIGURE	DATE	AGE (YEARS)	WEIGHT (POUNDS)	HEIGHT (INCHES)	COMPARISON WITH BALDWIN WOOD STANDARDS	NUMBER OF CARPAL CENTERS	
						GEORGE	PRYOR'S STANDARD (MALE)
3a	11/23/27	5	—	—	per cent	3	5 - 6
3b	4/ 9/28	5 $\frac{2}{3}$	60 $\frac{1}{2}$	45 $\frac{3}{4}$	+28	3 & 4	5 - 6
3c	1/13/29	6 $\frac{1}{6}$	65	49	+18	5	6 - 7
3d	11/25/29	7	63	49 $\frac{1}{4}$	+14	6*	6 - 7
—	10/12/31	9	74	53 $\frac{1}{2}$	+8	—	7

*Distal ulnae not yet evident.

Inquiry into the developmental history of George showed that he was born at full term, November, 1922 Delivery was normal and the presentation cephalic The birth weight was 7 pounds, 4 ounces The birth-cry was strong and there were no convulsions or cyanosis He was breast fed until 13 months of age, no additional food being added to the diet The infant was then given orange juice, cereals, cooked fruit, vegetables and meats, but never any cod liver oil His appetite was always poor The motor development of this child proceeded at a more rapid tempo than that of his older brother He sat up alone at about 6 months, never crawled, and was able to walk with support at 10 months and without support at about 15 months He spoke single words at one year and phrases at about two years The first tooth erupted at 10 months In general, he showed a much more rapid rate of development than his brother, a fact of interest in view of subsequent development of the carpal centers. He always enjoyed good health, although subject to occasional colds Tonsillectomy and adenoidectomy were performed at 4 years of age

Physical examination showed a rather well developed youngster weighing 40 $\frac{1}{2}$ pounds and 40 inches tall. The circumferences of his head, chest and abdomen were 19 $\frac{1}{2}$, 20 $\frac{3}{4}$ and 22 inches, respectively His color was good, the subcutaneous tissue firm and the muscles somewhat flabby He was a mouth breather and the facial expression was dull The posture was faulty, shoulders stooping, scapulae winged and the abdomen protuberant The hips were rather wide and there was some degree of knock knee The genitals were small and the penis retracted, but

both testicles were fully descended. There was a considerable amount of fat over the suprapubic region. The skin was soft, smooth and had normal lanugo hair. The hands were small and the fingers thin and tapering. The nails were normal but of dull appearance. The entire picture suggested a Froeblich type. In fact, when the boy was about seven years of age, he was observed elsewhere and considered a case of glandular dyscrasia and was given glandular therapy, but without apparent improvement in general physical state. At that time a basal metabolism test was made and was recorded as +9. He did poorly in school, his memory being poor, he failed of promotion. Socially and at play he preferred to associate with much younger children.

The face was full and round. The hair of the scalp was dark brown and coarse, the eyebrows and eyelashes were normal. The palpebral fissures were equal and the pupils reacted normally to light and accommodation. Subsequent examination, at 9 years of age, revealed a marked impairment of visual acuity, the vision being 20/100 for both eyes. The ear, nose and throat were normal. There were 20 deciduous teeth, showing poor enamel and wide spacing, the occlusion was good. Although at 4 years of age caries had not developed, examination at 7 years showed carious involvement of all deciduous molars. At 9 years the four permanent first molars were still sound. The neck was normal, there was no adenopathy. The chest was somewhat flat anteroposteriorly. The heart, lungs and abdomen were normal. The reflexes, both superficial and deep, were equal and active.

Summary—These histories may be summarized by the statement that the rate of development of the carpal centers of the older brother, L, was not only remarkably slow but was striking in the manner in which the retardation was corrected. As late as 8 years of age but two centers had appeared at the wrist and no progress had been made in this respect for two years. Suddenly during the ninth year, from winter to autumn, a spurt in ossification came about. Films taken in November of this year revealed the presence of 5 centers in the left and 6 in the right wrist in addition to now centers at the distal ends of the ulnae, the appearance of which had been delayed by approximately two years. No adequate explanation can be suggested to explain this sudden increase in ossification. The boy's height had remained the same, but his weight had increased 6 pounds and there was an undoubted improvement in his general condition. The younger boy, G, was never so marked a case of carpal retardation, having 3 carpal centers instead of 5 or 6 at five years of age. He caught up to the normal gradually, so that at seven years he approached closely to the standard except for a delay of the distal epiphyses of the ulnae. Whereas L was somewhat below the average for height-weight age, G was somewhat above, tending to be stout. His metabolic rate, however, was slightly above rather than below the average. It may be added, that the development of the carpal centers of both parents appeared normal.

DISCUSSION

It is true that variations may be noted in the development of carpal centers, a variability which is not great and, in our experience, is nullified by the second or third year of life. Some years ago it was shown

by Hess and Weinstock¹ that even at the time of birth two centers occasionally may be noted. It is also true, as noted at our institution, that there is a similarity between brothers and sisters in regard to the rate and stage of carpal development. The marked retardation observed in these brothers emphasizes the fact that congenital and constitutional factors play a rôle and must be considered in studies bearing on the physiology and pathology of calcification and ossification. In the paper just referred to the rôle of constitution was further emphasized by the fact that the carpal centers of negro infants, at birth, were further developed than those of white infants. A similar constitutional variation has also been brought out recently by one of us in connection with the susceptibility to rickets of puppies of different breeds², one breed being more susceptible than another. In other words, in experimental as well as in clinical rickets there may be a definite constitutional tendency to rickets, quite apart from diet, hygiene, and growth. This must be evident to all who have carefully studied rickets in the clinic. The interesting observation of Stettner to the effect that the carpal centers of urban children ossify earlier than those of rural children, may, perhaps, be interpreted in this way.³

This clinical observation also emphasizes the fact that although ossification of the skeleton depends on systemic factors, it is also dependent on one or more local factors. As stated, the calcium and inorganic phosphorus titer of the blood in these infants was normal, 10.3 Ca and 4.2 mg P in the one boy, and 10.0 and 4.0 mg in the other. The Ca \times P product was well within normal limits. Nevertheless, ossification was delayed for years and, in the case of the one came about suddenly in the course of a few months without apparent change. We attribute this delay, as well as its sudden correction, to the absence and to the rapid development of a local factor, of what may be termed a mordant or "Kalkfaenger". Without taking cognizance of a local factor of this kind, no satisfactory explanation is possible of "high phosphorus rickets" in infants. Occasionally, but by no means rarely, rickets develops in spite of approximately normal concentrations of calcium and inorganic phosphorus in the blood and a normal Ca \times P product. We have observed numerous cases of this kind, especially among young infants. The same may hold true for "rat rickets". In chickens it is very common to find calcium concentrations of over 10 mg, associated with phosphorus concentrations of 8 to 9 mg, in other words an exceedingly high Ca \times P product, and nevertheless the roentgen rays as well as histologic examination show the typical lesions of rickets and the total ash is far below the normal level. This interesting phenomenon, unexplained, and of undoubted importance in the physiology of ossification as well as in the pathogenesis of disorders such as rickets, is further illustrated by the cases of carpal retardation which we have reported.

CONCLUSIONS

An instance is reported of prolonged retardation in the development of the carpal centers in two brothers. A clinical observation of this kind is exceedingly rare and gains added interest due to the fact that it illustrates the rôle of congenital and constitutional factors in relation to ossification. As the concentration of calcium and inorganic phosphorus of the blood was normal it would seem that a local calcifying factor a mordant or Kalksaenger was lacking. In one of the cases the retardation was compensated suddenly during the ninth year within a period of a few months.

REFERENCES

- 1 Hess, A. F., and Weinstock M. *Am J Dis. Child* 29 347, 1925
2. Hess, A. F. and Blackberg N. *Am J Physiol* 102 8, 1932
- 3 Stettner F. *Arch f Kinderh* 68 342 1920
- 4 Prior, J. W. *Am J Phys Anthropol* 8 401 1925

ALIMENTARY TOXICOSIS

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NEW YORK, N Y

THE SUBJECT which I wish to discuss is one in which Czerny was a pioneer

Czerny¹ classified the nutritional disturbances of infancy on an etiologic basis under three headings *ex alimentatione*, *ex infectione* and *e constitutione*. The commonly accepted view of the etiology of alimentary toxicosis is that it is secondary to an infection, and so in Czerny's scheme it would be placed under the heading of *ex infectione*. This term signifies the following possibilities: that bacteria decompose food, causing it to become injurious, that bacteria normally inhabiting the intestinal tract may, through putrefaction and fermentation of the intestinal contents, bring about the presence of toxic or irritating substance or may themselves become injurious, and that bacterial infection, regardless of the portal of entry or location, whether enteral or parenteral, may lead to a nutritional disorder. In brief, it includes the nutritional upsets which are the results of bacterial infection or the products of bacterial proliferation.

This view is probably a correct explanation for the majority of cases of toxicosis. Patients have been observed, however, whose histories indicated that other inciting factors were responsible for the disturbances which lead to toxicosis. With some exceptions, these cases etiologically would fall under Czerny's headings *ex alimentatione* and *e constitutione*. Thus, pure digestive disturbances such as those arising from overfeeding or from exceeding the tolerance for fat, abrupt weaning of an infant from its mother's milk, constitutional conditions such as inherent intolerance for carbohydrates and allergic idiosyncrasies to foods, summer heat, especially when associated with increased humidity, direct gastrointestinal irritation such as that induced by cathartics, all have been known to initiate the gastrointestinal disturbance which resulted in the development of toxicosis.

Once the nutritional disturbance has been initiated, what brings about the toxicosis? The most convincing evidence points to the following explanations. The fluid (water plus minerals) loss, regardless of the manner in which it takes place, whether by diarrhea, vomiting, insensible perspiration (ventilation through lungs and skin), or by these combined, leads to blood concentration, impaired circulation, diminished renal function, and acidosis, factors which are responsible for the intoxication. Most authors recognize the importance of these factors and some have attributed special significance to the acidosis and retention products due to the renal hypofunction.

Another explanation of the pathogenesis of toxicosis which has been championed extensively is based on its similarity to histamine shock. It has been suggested that the origin of these histamine like substances is the upper intestinal tract where coli bacilli have migrated from below and caused partial splitting of proteins or by the disturbed intermediary metabolism, or from the injured liver. It has also been suggested that the injury produced by these substances takes place because the liver has been damaged and is no longer able to perform its function of detoxification. The evidence for much of the above is still theoretical.

To demonstrate our point of view on this subject the history abstracts of fifteen cases of toxicosis presenting a variety of etiologic agents, and treated in the children's wards of Mt Sinai Hospital according to a plan previously described will be presented and briefly discussed.

DISCUSSION OF CASE ABSTRACTS

Toxicosis ex Infectione—Case 1 had a positive stool culture for the Flexner dysentery bacillus and thus represents an enteric infection. Cases 2 to 5 were, respectively, due to mastoiditis, smallpox vaccination, pyuria and pyuria with recurrent upper respiratory infections. These illustrate toxicosis due to parenteral infection. It is noteworthy that in Case 5 patient was a breast fed infant. In the analysis of a group of 71 cases of toxicosis we found that infection was present in more than half. Undoubtedly some developed their infections after the diarrhea and vomiting had started. The Cases 1 to 5, however, illustrate a relatively common sequence, infection, gastrointestinal disturbance, toxicosis, and suggest a causal relationship between them.

Toxicosis ex Alimentatione—Case 6 developed within three days after weaning from the breast to a simple formula of pasteurized milk, sugar, and water prepared under hygienic conditions. In Case 7 patient failed to thrive on cow's milk formulae and at eighteen days of age developed diarrhea which went on to toxicosis. In Case 8, patient was well except for slight constipation, until orange juice was started. She received an ounce of orange juice on the first day and promptly developed diarrhea. In absence of infection or other factors which may have initiated the diarrhea in these cases, we believe that they exemplify the development of nutritional disturbances *ex alimentatione* which progressed to toxicosis.

Toxicosis c Constitutione—Case 10 was a child with cyclic vomiting. She vomited everything taken for a day, then developed diarrhea and rapidly went into toxicosis. In Case 11 patient while being treated for widespread eczema, lost twenty one ounces in two days and suddenly collapsed. He had vomited only a few times, toxicosis supervened. These cases illustrate the constitutional predisposition which

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In the past few years the therapeutic procedure which we have employed² has had as its desideratum the reestablishment of an adequate circulation and a rapid improvement of renal function. Coincident with this there occur detoxification, correction of the acidosis, improvement of the tissue turgor, and a gradual disappearance of the gastrointestinal dysfunction.

It is worthy of note that as early as 1906 Geheimrat Czerny announced a classification of nutritional disorders on an etiologic basis that even today encompasses the preponderant number of instances of this illness.

CASE 1—H. F. #31695, Forti, Klean, male, seven months of age. Admitted July 31, 1930. His birth and past history were normal. He was breast fed for two months then weaned on simple milk formula. He did well until three weeks before admission when he developed diarrhea with fever of 103° F. On a $1\frac{1}{2}$ milk— $1\frac{1}{2}$ barley water formula the diarrhea improved and the fever dropped. Two weeks later or five days before admission, the diarrhea recurred—14 to 19 stools daily. With this the child was brought in collapsed, dehydrated and toxic. His temperature was 106° F., he was drowsy, his eyes were glassy, his skin turgor poor, his pulse rapid and breathing slow and deep. The stools were bloody and on culture showed the Flexner type of dysentery bacillus. His blood CO content was 45 vol. per cent. He responded to treatment for toxemia slowly. His progress was interrupted by an acute respiratory complication. He was discharged well in thirty days.

CASE 2—M. M., #31,213, and 31843 was a nine-month-old Irish female baby who weighed five pounds when born at term. She did fairly well on a simple milk formula and orange juice. At seven months of age Aug. 7, 1930, she was admitted to the hospital because of anorexia, diarrhea and pyuria. She weighed 11 pounds. The diarrhea which did not respond to treatment with ordinary milk mixtures improved on protein milk. She was discharged as well after six weeks, with a formula of 20 ounces of milk, 10 ounces of water, $1\frac{1}{2}$ tablespoons of cane sugar, farina, orange juice and cod liver oil. A week later the child was readmitted because of acute rhinitis and severe diarrhea, vomiting, temperature 103° F., and irritability. She looked marantic and mentis ill. After a twelve-hour period of starvation and subcutaneous injections of saline solution she was started on a simple milk formula, and three days later it was changed to protein milk. She improved. Urine was normal. With onset of otitis media a week later the diarrhea recurred. The protein milk was reduced and the child was given two blood transfusions each of 110 c.c. one week apart. The child continued to do poorly, the diarrhea continued, the otitis media was worse, she lost a pound in twenty-four hours. Mastoidectomy seemed indicated but was delayed because death seemed imminent. On Oct. 29 she weighed 7 pounds, 2 ounces, temperature was 105° F., color was ashen gray, pulse was very weak, skin turgor was extremely poor, she became dyspneic and she showed evidence of severe blood concentration and acidosis. She was nine and one-half months old and weighed 7 pounds and 2 ounces. Treatment for toxemia was successful and no surgical intervention was needed for the otitis condition. At twelve months she weighed 12 pounds.

CASE 3—O. C., #39201, admitted Aug. 18, 1931, was an eleven-month-old Spanish female whose family history and past history were negative. She was normal at birth, breast fed for three months and did well thereafter. She was never ill before. At ten months she received diphtheria toxin antitoxin and at

TABLE I
LABORATORY DATA OF CASES REPORTED

CASE NUMBER	DATE	BLOOD		PLASMA		BLOOD		SÉRUM		SUGAR BLOOD	URINE
		HGB	R.B.C	NaCl	mg	Urea	N	CO ₂ CONTENT	PROTEIN		
2	10/29/30	99						10 vol %			alb few WBC
	10/31/30	80									
	11/ 0/30	99						50			neg
3	8/18/31	70	4500000	667	mg %			20			alb casts
	8/20/31							50			
	9/ 3/31	70	4880000	605				48			neg
4	10/30/32	78	5500000	590		97	mg	19.5			alb pus
	10/31/32			690		18		25		Serum Phosphorus 7.5	
	11/ 4/32	70		600		7		24		5.8	pus
	11/15/32			555		7		42		5.1 4 7.5	
5	11/29/31	70	3050000	538		58		17			WBC much pus
	12/ 2/31			400				31		7.0	
	12/12/31			580		9		46		6.3	much pus
	1/ 3/32			410		33		36.5		7.6	much pus
6	5/25/32	102	4000000	700		75		22			alb
	5/27/32					36		27		4.7	WBC
	5/29/32							55			
	5/31/32	95	4900000	585		18		51		5.8	neg

ten and one half months she was vaccinated against smallpox Nine days there after she began to have fever and simultaneously diarrhea

Her diet which consisted of whole milk (pasteurized), orange juice, vegetable and cereal, was redneed to barley and rice gruel

The temperature dropped in a few days, but the diarrhea continued, the stools were green and watery Shortly thereafter the stools became very numerous, the fever recurred, and vomiting started

On admission to the hospital the child looked ashen gray and collapsed Skin turgor was very poor, and she had marked hyperpnea and temperature of 105° F Her eyes were sunken and her pulse was poor The urine was scant, and contained albumin, a few granular casts and white blood cells Blood chemistry revealed acidosis and hypoglycemia

The vaccination was in scar stage and clean. No other evidence of infection was present She recovered rapidly

CASE 4—M K, #34420, admitted Oct 11, 1932, was an eight and one half month old female who was normal at birth and did well on artificial feeding until she was four months old when she developed a vaginal discharge Gonococcal infection was never demonstrated, nevertheless treatment was quite active with internal medication as well as local applications of antiseptic solutions She developed pyuria with recurrent elevations of temperature With her fever 100° to 102° F, she suffered anorexia and vomited frequently Her weight remained stationary for two months When she was eight months old, her stools became loose, her anorexia more marked and her general condition worse She was admitted for study of the genitourinary tract Intravenous urography revealed dilated ureters and calvees The p s p test showed very poor excretion—15 per cent in three hours—but at a later time as much as 55 per cent in three hours The blood chemistry was normal and the urine contained pus, but no casts or red blood cells She vomited frequently, causing her weight to be stationary

About five days after reflex urography was attempted, the child collapsed She became markedly hyperpneic (70 respirations per minute), cyanotic, her circulation was collapsed, skin turgor was poor, her dependent parts were mottled blue, and temperature mounted to 108.4° F She was unconscious, and had twitchings of the extremities, she was anuric, blood pressure was not elevated Blood showed evidence of severe acidosis, azotemia, and concentration.

CASE 5—L B, #332765, a five month old Jewish female child was normal at birth and had thrived until five weeks before admission to the hospital, when she began to be irritable, restless and took the breast poorly Stools became thinner and more frequent—5 to 6 daily—and she stopped gaining weight. About twenty four to forty eight hours before admission the stools became numerous, she refused to eat and became very ill. On admission she was drowsy, irritable, her cry was weak, her color gray, her eyes were sunken, her skin loose and pasty, of poor color, except over the lower extremities, hands and forearms, where the skin was edematous and pitted on pressure She had deep hyperpnea and a poor pulse The urine was scant and showed only few white blood cells Blood showed evidence of marked acidosis, azotemia and some concentration She improved under the treatment for toxemia The pyuria persisted

On treatment as a case of toxemia recovery was prompt However, in forty eight hours she began to dribble purulent urine Examination revealed a relaxed bladder and anal sphincter with some hypesthesia of the perineum Rectal examination revealed a mass at the sacrum Her knee jerks and abdominal reflexes were normal. The urinary tract was examined by various methods including intravenous pyelography and cystoscopy and revealed cystitis The mass felt by rectum grew and caused a defect in the sacrum, seen on roentgen ray examination.

The above episode recurred several times in the subsequent ten months but was not accompanied by diarrhea. Vomiting did occur once or twice a day. The same treatment was effective each time. Blood pressure was never elevated. Eye grounds were normal. Although she had the chronic pyuria, no evidence of nephritis or renal insufficiency was demonstrable except for the oliguria during these recurrent episodes of toxicosis. She was found dead in bed without any apparent cause at fifteen months. Postmortem examination revealed cystitis and a lipoma involving the sacrum and cauda equina.

CASE 6—R. M. #330060 admitted Mar 2, 1932. A two-month-old Irish female child weighed 7 pounds 8 ounces at birth and 10 pounds 12 ounces four days prior to admission when she was weaned to a formula of 2½ ounces of milk 1½ ounces water and two teaspoons dextrinmaltose every three hours. The milk was grade A and boiled. She vomited the first feeding the formula was changed slightly but diarrhea started soon thereafter. The diarrhea was profuse a stool every fifteen to thirty minutes and continued so until the day before admission when the formula was changed again. However the diarrhea continued and the child became drowsy. On admission she looked lethargic toxic gray. Respirations were deep and 54 per minute. Skin was mottled and its turgor very poor. The urine contained albumin, and the blood revealed concentration with acidosis and azotemia. On treatment for toxicosis she made a rapid and complete recovery.

CASE 7—A. S., #325913, was a male Italian twenty-six days old. His birth weight was 7 pounds and he was a difficult feeding problem. On a formula of cow's milk, sugar and water he developed severe diarrhea at eighteen days and lost 2 pounds in the next week. On admission Aug 9 1931, he was ashen gray dehydrated thin marantic anpathetic, and collapsed. His hands and feet were twitching. A lumbar puncture revealed normal spinal fluid. He was treated with a saline solution clysis a blood transfusion and a small amount of formula of evaporated milk without success. His blood CO content was 12.5 vol. per cent, the NaCl was .02 mg per cent and the hemoglobin 92 per cent. Under the routine treatment for toxicosis he promptly improved excepting for the diarrhea which lasted seven days.

CASE 8—R. G., #320472, admitted Aug 26 1931. A Porto Rican three months of age. She was breast fed for two months then weaned on a condensed milk formula. She thrived but was constipated for which orange juice was recommended. A tablespoon of orange juice was given twice in one day. The next day the child began to have diarrhea which had continued for the past two weeks increasing to 8 to 10 green watery stools daily. She lost two pounds in that time and went progressively downhill.

On admission she was moderately ill, slightly lethargic, irritable. Her eyes were lusterless. Her liver was 2.5 cm below the costal margin, and she had marked craniotabes. She was treated by starvation and simultaneous saline injection for about twenty four hours, during which time she became collapsed. Respiration became slow and deep, and the blood showed marked concentration and acidosis and evidence of rickets. Treatment for toxicosis was instituted, and after a stormy course for three days with almost constant convulsions, she improved and made a complete recovery. During the convulsive state her Chvostek reaction was quite active and 10 c.c. of calciom gluconate given intravenously caused no improvement. A lumbar puncture revealed xanthochromic fluid.

CASE 9—R. B., #336066 admitted Feb 6, 1932, was a Jewish female fifteen months old, who was normal at birth and did well except for two episodes of recurrent vomiting at three months and again at six months of age. Both were

stopped by enemata. She developed well, had been vaccinated and injected with diphtheria toxin antitoxin

Three days prior to admission she suddenly began vomiting everything, including water. The next day her temperature rose to 102° F, and diarrhea started. She had 5 or 6 loose stools in twenty four hours and then became quite drowsy. Temperature rose to 104° F, color became gray, eyes sunken, skin turgor poor, pulse very rapid and weak, and respirations quite slow and deep. A diagnosis of toxicosis was made, and she was promptly treated with success. Urine contained albumin, acetone and in occasional white blood cells. Blood revealed a lowered CO₂ content, diminished sodium chloride, and a somewhat elevated blood sugar.

CASE 10—R J, #318774, admitted Sept 27, 1930. A Porto Rican eight month old male child admitted because of eczema which had appeared at three months of age when he was weaned, and covered his entire body. He had pertussis at six months of age. While in the hospital being treated with a tar ointment, he was fed a simple formula of pasteurized milk, cereal, and orange juice, a diet similar to that which he had had at home. His entire body was covered with this ointment for a few days. The eczema improved, but anorexia developed. Treatment for eczema was stopped. He vomited two or three times in the next four days and lost twenty one ounces. He was found in collapsed condition, skin turgor was poor, eyes were sunken, breathing rapid and labored, and pulse very poor. He was in a semistuporous state. Treatment for toxicosis was instituted with prompt improvement.

CASE 11—M McK, #328830, admitted Aug 6, 1931. A two month old Irish female was normal at birth at term weighing 7 pounds 2 ounces. She was exclusively breast fed for three weeks and continued to thrive on a complementary formula of 12 ounces of grade A milk, 8 ounces of water and 1 ounce of sugar. Orange juice was started at one month. Eighteen hours before admission, during very hot humid weather, she began to have diarrhea. She had 12 loose, foul smelling stools in that period. Barley water was ordered in place of milk, but vomiting followed and the diarrhea continued. On admission she was collapsed and toxic, temperature was 102° F, skin was gray, mottled, and of poor turgor, eyes were sunken, and she was lethargic and markedly hyperpneic. There was no evidence of infection. Physical examination revealed no infection. The blood showed evidence of acidosis. The stool culture showed *Bacillus proteus* and *Bacillus coli*. She responded to the treatment for toxicosis.

CASE 12—F P, #329631, an eleven month old Porto Rican female was admitted during the hot spell, on Aug 31, 1931. She was prematurely born and weighed 3 pounds 3 ounces. She was breast fed for three weeks, then fed an evaporated milk formula until six months of age, and since then 6 ounces of grade A milk and 2 ounces of water four or five times a day, cereal, occasionally orange juice but no cod liver oil. For the past two days for no apparent reason, the child began to have diarrhea—12 stools daily—and vomited a few times. In the past twelve hours she had become quite drowsy. On admission she was very ill, pale, eyes were sunken, skin turgor was poor, abdomen scaphoid, and breathing very slow and deep, pulse was very weak. There was no evidence of infection. Blood showed evidence of anemia, severe acidosis, azotemia, and blood concentration. The stool culture showed *Bacillus coli*. She did well on the treatment for toxicosis.

CASE 13—J C, #336294, admitted March 13, 1932, was normal at birth, weighing 10 pounds. He was breast fed for three and one half months and did well. Since then he thrived on a formula of milk and oatmeal water. He had no orange juice or cod liver oil. Two weeks before admission he began his first illness with coughing. After the first week he improved, only to get worse again two days

later with heavy breathing paroxysmal cough and occasionally vomiting and temperature of 100° F. Because of the productions of mucus with the cough castor oil was given and in the subsequent twenty four hours the child developed severe diarrhea. He was admitted the next day with temperature of 100° F., neutely ill, markedly dehydrated moderately toxic eyes sunken, fontanelle depressed and the skin turgor very poor. He was hyperpneic coughed and had dullness and râles at the left base which proved to be due to pulmonary involvement, on roentgen ray examination. Blood showed evidence of acidosis and blood concentration and the urine contained albumin. He responded well to the treatment of toxemia without a blood transfusion. The rise in temperature lasted only three days.

CASE 14—M. M., #343 G., a five-month-old Irish female child was admitted on Sept. 23, 1932, because of diarrhea for one week. It had started after a dose of milk of magnesia given to her because the previous few stools were too firm. She was quite sick, apathetic and irritable. Her skin turgor was poor the eyes sunken the fontanelle depressed and the pulse poor. Blood showed evidence of marked concentration, mild acidosis and azotemia and hypoglycemia. Her stool culture yielded *Bacillus coli enterococcus*. Urine showed some albumin and an excess of white blood cells. She was treated as a case of toxemia with prompt and progressive improvement.

CASE 15—J. R., #343 H., admitted Nov. 6, 1932. A five-and-one-half-month-old Jewish female was admitted because of periodic abdominal cramplike pains, vomiting and bloody diarrhea for forty-three hours. She was in poor condition but was operated upon for intussusception which was found at the cecum and released. Having been breast fed exclusively she was then fed small amounts of milk obtained from her mother. Her condition was fair for a few days. She then developed upper abdominal distention vomited bile-stained material, and passed very little gas and no stool by rectum. The temperature fluctuated from 101° to 103° F. Blood culture was sterile. She became toxic eyes were sunken color gray, skin turgor poor, cry weak and pulse very poor. The epigastrium was distended. Blood showed evidence of concentration and azotemia, but no acidosis. She probably had intestinal and gastric atony. She was treated as a case of toxemia except that her stomach was lavaged about eight or ten times in four days, with progressively diminished evidence of retention. She recovered promptly and completely under this treatment. Blood CO₂ content dropped from 54 to 39 vol. per cent after two days of treatment.

REFERENCES

1. Czerny, A., and Keller, A.: *Des Kindes Ernährung Ernährungsstörungen und Ernährungstherapie* 16., Franz Deitke.
2. Karelitz, S., and Schiek, B.: *Am J Dis Child* 42: 781, 1931. *J A M A* 99: 366, 1932.

1097 PARK AVENUE.

MEASLES IN NEWBORN INFANTS (MATERNAL INFECTION)

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FOUR cases of measles in young infants who were infected by their mothers have been treated in the last two years at the Willard Parker Hospital. The ages of these infants at the time of onset of measles was fourteen, fourteen, and thirty days, and ten weeks, respectively. In two of the cases, therefore, the mother was incubating measles at the time of the birth of the child. Both of these children were born in institutions. In one case, the mother's first day of fever was five days postpartum, and in the second three days postpartum. The offspring had fever on the ninth and tenth day, respectively, after the onset of the mother's illness. The following day, Koplik spots and other clinical signs of measles were noted in both infants. The day after, the rash appeared.

The incubation period of measles is usually given as from eleven to fourteen days after exposure. This incubation period takes into consideration only the first appearance of clinical symptoms, such as cough, coryza or the first appearance of the rash. However, if the child is in an institution at the time of exposure, or soon thereafter, the temperature is taken regularly, and the first day of fever may be considered the day of onset. This temperature rise occurs about the ninth or tenth day after exposure and this may be called the true incubation time.

In Cases 3 and 4 the mothers were exposed to measles postpartum. In Case 3, the mother's exposure took place eleven days postpartum. Twelve days later she had her first symptoms. Eleven days after, when mother and child were admitted to the hospital, the child already had fever and a few Koplik spots. In case four, the time of the mother's exposure was not known. Her first symptoms of measles were present three days before her admission to the hospital. Eleven days later the child developed fever. The next day Koplik spots were seen.

It seems, therefore, that the incubation period of the children whose mothers were incubating measles at the time of birth and those that were infected postpartum is about the same. The first day of fever was from nine to eleven days after exposure.

The clinical course of the measles in these infants apparently differed in no way from that seen later in the first year. In case one, the child received convalescent serum on the seventh day after exposure. The course of the measles was mild. In this case it can hardly be considered

From the Willard Parker Hospital for Contagious Diseases. Dept. of Hospitals
New York City

TABLE I

CASE NO.	BORN	DATE OF FIRST DAY OF FEVER		INCUBATION OF CHILD	AGE OF CHILD AT TIME OF MEASLES	COURSE OF MEASLES
		MOTHER	CHILD			
1	4/16	4/21	4/10	9 D	14 D	Not very sick
2	2/20	3/ 3	3/13	10 D	14 D	Very sick
3	3/ 8	3/23	4/ 7	10 D	30 D	Otitis, Pneumonia
4	1/13	3/13	3/24	11 D	10 W	Quite sick
						Pneumonia
5	1/ 2	12/26				Quite sick
						Otitis media
						Pneumonia
6	3/14	3/ 8				Mother had full rash at birth Child isolated immediately No serum given No measles
7	1/23	1/26				Rash receding when child was born Serum given when 1 day old No isolation. No measles
						First clinical sign of measles 8 days post partum Serum given 8 days later No measles
8	11/20/32	2/23	3/10	16 D	4 M	Whole blood given 9 days after exposure Mild

D—Day
W—Week
M—Month

proof of the efficacy of convalescent serum as the correct time for giving serum is within five to six days after exposure. In the other three cases in which serum was not given, the children were seriously ill. All three had symptoms and signs of pulmonary involvement and two developed a purulent otitis media. The fever lasted from ten to eighteen days after the onset. All of the children recovered.

There were three additional cases, none of which developed measles that should be included in this series.

Two cases (No 5 and 6) can be considered together. Both children were born while the mother had clinical signs of measles. In Case 5, the child was born when the mother's rash was at the maximum stage. The newborn showed no clinical evidence of measles. No convalescent serum was given, but the child was immediately isolated from the mother. The isolation was maintained until the child was ten days old. The child did not become infected. In Case 6 the child was born while the mother's rash was receding, that is about two days after the maximum stage. This latter child also showed no clinical signs of measles at birth. The child was given convalescent serum soon after birth and was not isolated from the mother. This infant also remained free of measles.

In Case 7 the mother was incubating measles when the child was born. Her first day of fever was three days postpartum, but she had no

clinical signs of measles until six days later, when for the first time her temperature was over 38.5°C (101°F). The child was given 10 cc of measles convalescent serum when seventeen days old. This was eight days after the mother's first symptoms. Although the serum was given late, the child remained free of measles.

COMMENT

As has been shown by Herrman¹ and others, when a mother has had measles previous to pregnancy, her infant usually has an immunity for at least the first five months of life. This immunity is presumably transmitted through the placental circulation. It is often stated that if the mother has not had measles, the child has no such immunity. Since in most large communities the mother has had measles during childhood, measles in very young infants is infrequent. But this rule of immunity is not infallible, and there must be differences in individuals. I observed one infant three months of age, exposed to measles in the mother, who did not contract the disease. No convalescent serum was given. This child has been followed for seven years and up to the present time has not had measles.

A review of the literature of congenital measles, or the measles of early infancy is unnecessary. This has been adequately done by Reuss,² Canelli,³ Mariani,⁴ Debie and Joannon⁵ and others. These authors report cases in which the mother had measles a few days before expected delivery. In most of the cases the child had clinical signs of measles at birth. The measles was usually at the same stage as that of the mother. In some cases, however, the measles would be at a later stage. This suggests that the fetus is infected at the same time as the mother or is infected during her incubation period. This, however, was not our experience. In the two cases in which the children were born while the mother's measles was still active, neither child showed any evidence of having been infected in utero. Immediately after birth, one was given convalescent serum and allowed to remain with its mother, while the other was given no serum but was isolated. They both remained free of infection. Reuss² cites a case of Kolit in which a child had symptoms of measles five days postpartum, which was eight days after the onset of the mother's infection. The case reported by Laur⁶ the mother had symptoms the day after birth, the child's first symptoms appeared when it was eight days old. Reuss² also cites a case of Moser, in which the child was born after the mother's rash had faded and the child had its first symptoms fourteen days postpartum. In the three cases reported in this paper, in which the mother was incubating measles at the time of birth, two were subsequently infected. In one, the first day of fever was nine days, and in the other, ten days after maternal exposure. The giving of a large quantity of convalescent serum may have protected

the third patient. The case of Moser and those cases here reported were probably infected postpartum.

If the measles occurs before the eighth month of pregnancy the likelihood of a miscarriage or premature birth is great. This usually occurs at the height of the eruption. In such cases the fetus has been found to have a rash at about the same stage as that of the mother. Cutworth⁷ states that if the mother does not miscarry the offspring acquires a permanent immunity. Mariani⁴ cites several cases in which such offspring have been repeatedly exposed to measles and no infection has resulted. It would be interesting therefore to follow the cases here reported in which the infants were born while the mothers were still in the eruptive stage. Will they become infected on subsequent exposure? In contradiction to this are the well known cases in the Faroe Islands. During an epidemic of measles in these islands in 1846 a number of pregnant women were infected. The islands were practically free from measles until 1882 thirty six years later. At that time a number of the offspring of these pregnancies contracted measles.

The clinical course of measles in these young children infected by their mothers is usually severe. Mortality statistics comparable to the cases here described are very meager. Figures given by Debre and Joannon⁸ and Mariani⁴ show that the mortality is about 15 per cent. It seems logical, therefore in order to modify its severity that measles convalescent serum or adequate amounts of whole blood or serum from adults previously infected with measles should be given soon after exposure. It is known that in older children if immune serum is given within five or six days after exposure the measles may be aborted or the resultant measles may be mild. Up to the present time except for the case (No. 6) here reported I know of no newborn children infected by their mothers who have been given convalescent serum within five days after exposure. One cannot say with certainty therefore that this treatment will be efficient.

There is reason to believe that immune reactions in young infants are not the same as those occurring in older children. This is illustrated by diphtheria in young infants. It is usually serious and infants do not respond to treatment with antitoxin even when it is given early in the disease. Brindeau⁹ cites an epidemic of puerperal fever for which the diphtheria bacillus was responsible and states that nine infants were infected and all but one died notwithstanding antitoxin treatment. After this he injected each infant at birth with diphtheria antitoxin and the epidemic was arrested at once. Rabedeau, Dumas, Loiseau and Lacomme and others have attempted immunization of infants under four months of age with diphtheria toxoid and toxin antitoxin, but have been unsuccessful. The Schick test six months later was positive and the immunization had to be repeated in the second half of the first year.

The injection of toxoid into pregnant women did not influence the anti-toxin content of the newborn. Whether this analogy can be carried over to measles can only be decided with a wide experience.

SUMMARY

1 Four cases of measles in young children infected by their mothers are reported. In two of the cases the mother was incubating measles at the time of the birth of the child.

2 In one other case, in which the mother was incubating measles at the time of birth, the child was evidently protected by convalescent serum.

3 Two children were born while the mother was in the eruptive stage of measles. Immediately after birth, one received convalescent serum and was allowed to remain with its mother, and the other received no serum, but was isolated. Both remained free of measles.

4 Congenital measles and measles in early infancy has been discussed.

5 Since the course of the measles in young infants is usually severe the use of measles immune serum soon after exposure is indicated.

NOTE.—An additional case (No 8) was observed after this manuscript had been completed. A child three months old was exposed to measles by the mother. The father had had measles, and the child was given 25 cc of his blood, nine days after exposure. Fifteen days later the child showed symptoms of what proved to be modified measles.

REFERENCES

- 1 Herrman, C. New York State J M 23 404, 1923
- 2 Reuss, A. R. Die Krankheiten des Neugeborenen. Berlin, J. Springer, 1914, p 435
- 3 Canelh, A. F. Rev franc de pédiat 5 668, 1929
- 4 Mariani, J. A. Le Rougeole Congénitale, Paris Thesis, 1925, No 45
- 5 Debre, R., and Joannon, P. La Rougeole, Epidémiologie, Immunologie Prophylaxie, Masson et Cie, 1926
- 6 Laur, H. G. Zentralbl f kinderh. 17 118, 1912
- 7 Gutwirth, A. Casop lek česk 68 1402, 1929
- 8 Brindeau, M. S. Bull Acad d méd. Paris 86 191, 1921
- 9 Rabedeau Dumas, L., Loiseau and Lacomme. Bull. et mém Soc méd. d hôp de Paris 119 1121, 1925

55 EAST EIGHTY SIXTH STREET

OBSERVATIONS ON THE NATURE AND TREATMENT OF DIARRHEA AND THE ASSOCIATED SYSTEMIC DISTURBANCES

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THE large amount of work which has been done during recent years on the subject of infantile diarrhea and its effects on the body has served to bring out essential facts which have formed the basis for prophylaxis and treatment. The numerous discussions as to whether infantile diarrhea is due primarily to abnormal chemical composition of the food, to nutritional disturbances, to enteric infections or to parenteral infections have made it evident that there is no one cause of the condition, but that it may be due to any one or more of the factors mentioned, either alone or in combination with other factors. It has also become apparent that the severe toxic symptoms, the so-called "allimentary intoxication," are the secondary results of disturbance in the chemical equilibrium of the body brought about as the result of loss of water, salts and organic material by way of the gastrointestinal tract, and that the development of the clinical picture of intoxication depends more upon the degree and severity of the diarrhea than upon the nature of the underlying cause. Any severe diarrhea, whether occurring as the result of enteric or parenteral infection, or other causes, may be associated with the development of the symptoms of "intoxication." The picture may, of course, be complicated by the direct effects of any infection which is present.

The present day clinical picture of diarrhea and its complications differs materially from that of a decade or two ago. General improvement in milk and water supplies and more adequate supervision of infants and the education of mothers have resulted in a greatly decreased incidence of the specific enteric infections (dysentery). A better knowledge of the nutritional requirements of infants has resulted in generally better nutrition among infants, so that the effects of diarrhea are less serious. A better understanding of the nature of the condition and associated changes brought about in the body has resulted in a more intelligent application of specific therapeutic procedures designed to restore normal conditions in the body. Severe manifestations are more frequently checked in their incipency.

The purpose of the present paper is to summarize observations which we have made during the three-year period 1930-32 on all cases of diarrhea observed in the St. Louis Children's Hospital with the idea of determining the essential etiologic factors involved, and to evaluate the results of therapeutic procedures adopted.

During the three-year period 318 cases of diarrhea were observed, and of these 118 or 37 per cent fell in the classification of enteric infections or dysentery, using the term in its broadest sense to include not only infection with the recognized strains of dysentery, but also closely related organisms of the dysentery-paratyphoid-colon group generally recognized as pathogenic. As dysentery were included all cases in which specific pathogenic organisms were isolated, either from the stools during life or from the intestinal tract at autopsy, all cases in which specific agglutinins to the members of the dysentery-paratyphoid-colon group were demonstrated in the blood, and all cases in which there was clinical evidence of dysentery, such as blood or pus in the stools or a history of proved coincident familial infection. Even though all doubtful cases were included in the dysentery group, the relative incidence of dysentery is seen to be low as compared with other types of diarrhea. These figures differ materially from those of observers in other localities^{1, 2, 3} during the same years. There was observed the usual seasonal incidence, cases of this type beginning to be numerous in June and increasing in numbers to a peak in August and September, rapidly decreasing in numbers with the beginning of winter. (See Chart 1.)

In the series of cases classified as dysentery, parenteral infections occurred during the course of the disease and complicated the picture in 66 per cent of the cases. The most frequent infections were bronchopneumonia, otitis media, mastoiditis and pyelitis. The mortality in the group with complicating secondary infections was 28 per cent, in those uncomplicated by such infections, 10 per cent. The occurrence of dysenteric infection seemed to bear but little relationship to the state of nutrition of the infants, dysentery was observed in well nourished as well as in poorly nourished infants. Very few of the dysentery patients had been under adequate medical supervision, or were from homes in which there was an intelligent appreciation of hygiene.

The cases of nondysenteric diarrhea were most frequently observed during the early fall months in the case of infants whose nutrition had suffered during the summer season and who, with the beginning of fall, contracted upper respiratory infections which served as the final precipitating factor. The seasonal incidence differed somewhat from that of the dysentery cases. Some increase occurred during the warmer seasons of the year, and the symptoms were somewhat more severe in excessively hot weather, presumably because of the influence of

heat in favoring further dehydration, but a fair number of cases occurred even during the winter months when there were no cases of dysentery (See Chart 1)

In the group of cases of simple diarrhea definitely recognizable parenteral infections in the rhinopharynx, ears and mastoids were present in 83 per cent at the time of admission to the hospital. The incidence of such parenteral infections has however varied from year to year. During one fall and winter season previous to the present studies acute middle ear or mastoid infections immediately preceded the development of diarrhea in 93 per cent of the cases. The incidence of parenteral infection was really somewhat greater than the figures given would indicate. Not infrequently in the case of infants admitted to the hospital in a state of severe dehydration the presence of middle ear infections was unsuspected because of lack of evidence of

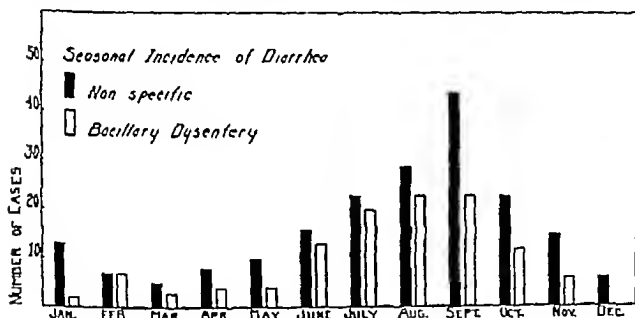


Chart 1—Seasonal incidence of non specific diarrhea and dysentery

inflammatory change in the tympanic membranes. With the restoration of the fluid balance and consequent improvement of the circulation, the tympanic membrane showed changes definitely indicative of infection, and this was confirmed by the obtaining of pus on paracentesis.

Nondysenteric diarrhea was observed much more frequently in undernourished infants, the course was more severe, the secondary toxic manifestations were more marked and the mortality was higher than in the case of well nourished infants. The most frequent feeding error preceding the development of diarrhea was quantitative or qualitative underfeeding which had led to impairment of the nutrition and apparently to lack of resistance to infection. The severe types of diarrhea were observed almost exclusively in artificially fed infants and in those who had received relatively dilute formulas of unacidified milk.

The mortality in the group of cases associated with parenteral infections was 85 per cent, over three-fourths of the deaths (77.4 per

cent) being directly attributable to the complicating infections rather than to the effects of the diarrhea per se

There still remained a small group of cases (17 per cent) in which neither enteral nor parenteral infections could be demonstrated. The cases in this group were characterized by a short duration of the diarrhea (average four days) and a low mortality (5 per cent), as compared with an average duration of fifteen days and a mortality of 35 per cent in the group with parenteral infections.

A study was made of the acidity and bacterial flora of the gastric contents in 200 of the cases of diarrhea of various types. In making

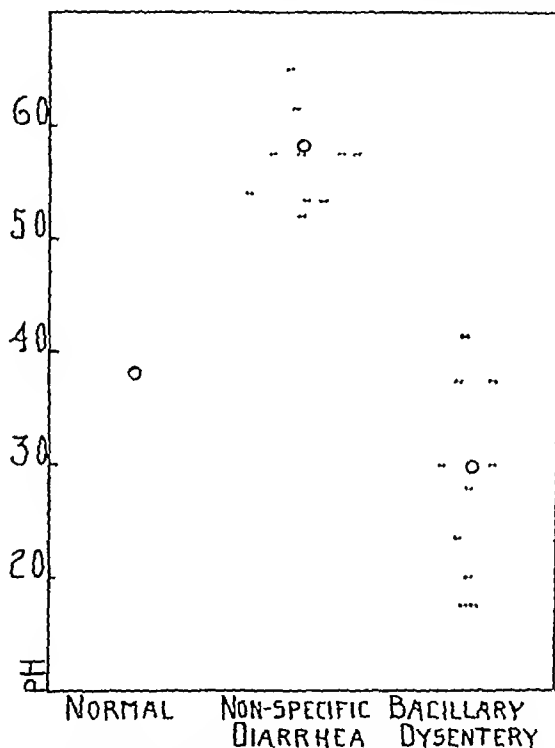


Chart 2—Hydrogen ion concentration of gastric contents. Each dot represents one infant. Circle represents the average for age group.

the observations, each infant was first given a test meal consisting of a 1:1 dilution of boiled whole cow's milk with water. Gastric contents were removed by catheter one and one half hours after the ingestion of the test meal. All samples containing mucus were discarded. Successive observations were made at the same time each day to note the effects of various feedings and other factors on the acidity and bacterial flora of the gastric contents.

The hydrogen ion concentration of the gastric contents was determined by the method previously described by Marriott and Davidson⁴

and bacterial cultures were made on each sample. The results were compared with those obtained from a group of normal infants under the same conditions. The P_{H} of the gastric contents of normal infants averaged 3.70 with extreme variations from 2.0 to 5.0. The results are expressed in graphic form in Chart 2. In the group of cases of non-dysenteric diarrhea, there was a distinct lowering of acidity, the average P_{H} being 5.65 and the extreme variation from 4.6 to 6.5. (See Chart 2.)

The acidity of the gastric contents of the cases in the dysentery group differed markedly from that of the nonspecific type associated with parenteral infections. Regardless of the age of the patient and of the specific organisms there was a distinctly greater acidity, the average P_{H} of the gastric contents being 3.0 only one third of the



Chart 2.—The incidence of *B. coli* in the gastric contents at varying hydrogen ion concentrations

cases having a P_{H} above this average value (Chart 2). The acidity of the gastric contents of the infants in this group was not only much higher than that observed in the noninfectious group, but also distinctly higher than that observed in the normal group. In some instances at the very beginning of the symptoms of dysentery there was some lowering of acidity, but after the first day or so the acidity almost invariably increased.

The bacterial flora obtained on culture of the gastric contents of both normal infants and those suffering from diarrhea almost always included staphylococci and often streptococci and yeasts. In none of the normal infants were any strains of the colon group observed. In 45 per cent of the cases of nondysenteric diarrhea the predominant flora of the gastric contents consisted of strains of *B. coli*. In a number of cases of parenteral infection associated with vomiting, *B. coli*

were cultured from the gastric contents before symptoms of diarrhea had developed, but in all such cases diarrhea occurred shortly afterward

A fairly close relationship was found to exist between the degree of acidity of the gastric contents and the presence of organisms of the colon group. This relationship is shown graphically in Chart 3. It will be observed that with decreased acidity there occurs an increased incidence of *B. coli*.

In marked contrast were the bacteriologic findings in the cases of dysentery. In these cases with the usual high gastric acidity, the stomach contents were entirely sterile in a few instances, and in the remainder the only flora present were those observed in the case of normal infants. There was a significant absence of members of the colon group during the active course of the disease. During the third week of the disease in protracted cases and where the picture was complicated by severe infections and malnutrition, a decrease in acidity of the stomach contents associated with the presence of *B. coli* was occasionally observed. In these cases, nondysenteric diarrhea appeared to have been superimposed upon a dysentery.

Our findings on the bacterial flora of the gastric contents are confirmatory of the observations of others,^{10, 11} and lend support to the hypothesis of enterogenous infection of the upper intestinal tract as a causative factor in the production of diarrhea. The observations on the relationship of gastric acidity to the presence of flora of the colon group indicate the possible mechanism of such enterogenous infections, and at the same time point the way to possible means of prevention and treatment of this type of diarrhea. We consider it probable that infestation of the duodenal and jejunal contents with *B. coli* and related organisms is of greater pathogenic significance than the presence of these organisms in the gastric contents. The presence of such organisms in the stomach, we take merely as evidence of more or less massive infection of the duodenal contents and recognize the fact that even in the presence of duodenal infection and in the absence of regurgitation, the stomach may be free from the organisms. When they are present in the stomach, however, it is most unlikely that they should be absent from the duodenum. As will be shown subsequently, it is possible through the feeding of buffered acid solutions to bring and maintain the gastric acidity to almost any desired degree within normal limits, and that such a procedure results in general in a disappearance of *B. coli* and exerts a favorable effect on the course of diarrhea of the nondysenteric type.

So far we have considered only certain conditions existing in the intestinal tract in the presence of diarrhea. The general effects of diarrhea upon the body are of as great or greater importance.

The failure to absorb ingested food substances and water from the intestinal tract and to reabsorb gastrointestinal secretions may lead

to serious disturbances in the body, the degree of which in an untreated case, is more or less directly proportional to the severity of the diarrhea. Such changes include (1) dehydration (2) electrolyte imbalance and (3) starvation each of which may lead to secondary trains of disturbances, the resultant of which may be rapidly fatal.

Apparently under normal conditions the total daily amount of gastrointestinal juices secreted and absorbed exceeds two- or threefold the fluid intake. The immediate source of water for these secretions is, of course, the blood plasma. When such secretions fail to be returned to the circulating blood, because of loss through diarrhea the volume of the plasma tends to diminish (anhydremia). Passage into the circulating blood of the intercellular fluid of the body and to a certain extent also the intracellular fluid particularly of the muscles may prevent for a time such shrinkage of plasma volume but when these reservoirs become exhausted, dehydration of both the tissues and the blood plasma results.

In addition to loss of fluid by way of the intestinal tract further water loss occurs as the result of evaporation from the skin and lungs. A diminished blood volume particularly when associated with increased viscosity due to the relative increase in the plasma protein concentration and cell volume results in a greatly diminished volume flow of the blood which in turn interferes with the normal function of the circulation in carrying oxygen and food substances to the cells and removing carbon dioxide and other waste products. Secretion of urine in particular may almost completely cease under such circumstances, and result in retention of urea and other waste products in the blood. During such periods of severe dehydration however there seems to occur a relatively much smaller reduction in the amount of secretion of gastrointestinal juices, a fact in keeping with the tendency for continued secretion of gastric juice in the experimental animal dying from gastric fistula, and of pancreatic juice in the animal succumbing to the effects of continued loss of pancreatic juice by fistula or intubation of the pancreatic duct.

Although perhaps the normal mixture of gastrointestinal secretions may have an electrolyte composition similar to that of the normal body fluids the loss of large amounts of gastrointestinal secretions by fistula or diarrhea almost invariably leads to electrolyte imbalance in the body fluids. This disturbance is usually such as to produce acidosis. Factors contributing to the production of acidosis are (1) a greater loss of fixed base than fixed acid (2) the inability of the kidneys to excrete enough fixed acid bound to ammonia to maintain a normal bicarbonate concentration in the blood, and (3) the occasional production of organic acids such as lactic acid and the ketone acids due to circulatory failure or to starvation. It should be remembered in this connection that analysis of a blood sample at a time when

severe dehydration exists sometimes fails to reveal loss of individual ions, i.e., there may be considerable chloride and fixed base lost from the body, and yet their concentrations in the plasma may be above normal. This is simply due to the fact that water has been lost from the plasma to an even greater degree. Recovery from such changes demands the proper administration, not only of water, but of chloride and base. When bicarbonate lowering is extreme (to $\frac{1}{4}$ or less of the normal concentration) the acidosis is frequently uncompensated, and the P_H of the blood may drop to 7 or less. Such severe acidosis tends promptly to be fatal and demands very vigorous treatment. Detailed studies of the chemical composition of the blood of patients observed and treated in this clinic have been published previously.⁹

In addition to the loss of water and electrolyte substances, there occurs a more or less rapid consumption of the body stores of carbohydrate, fat and protein, leading to emaciation, as well as to dehydration. Depletion of carbohydrate stores sometimes contributes to the development of acidosis in making ketosis possible. Ketosis, however, is not an important consideration in the acidosis of acute diarrhea, except when the diarrhea is due to acute bacillary dysentery. The consumption of body protein, however, may frequently lead to serious secondary disturbances, particularly when the plasma proteins become depleted. Such depletion, often masked during the period of dehydration, becomes manifest after restoration of body fluids, and contributes frequently to generalized edema, which quite aptly has been termed "nutritional edema." During the development of such edema, despite the fact that the kidneys may be essentially normal, there may occur marked oliguria, sufficient to impair seriously normal renal activity. Such renal activity may in turn result in continued electrolyte imbalance and interfere with recovery from acidosis or alkalosis.

Effective treatment of the more severe cases of diarrhea must include prompt restoration of normal blood chemical composition and normal conditions in the gastrointestinal tract. Measures particularly directed toward one end frequently have a good effect on the other, and the two objectives cannot be sharply separated one from the other.

In practice, we have found the following method of treatment to be the most effective: (1) total restriction of food, (2) the administration of an isotonic solution of sodium γ -lactate, sufficient to relieve promptly the acidosis and to relieve at least partially the dehydration.¹⁰ In the presence of severe acidosis, the usual dose of sodium lactate is 10 c.c. of a molar solution* per kilogram of body weight,

*Molar sodium lactate may be prepared by neutralizing 100 c.c. of U. S. P. lactic acid with concentrated sodium hydroxide, using phenol red as an indicator. The solution is made up to about 800 c.c. with distilled water and heated to the boiling point for from thirty to forty-five minutes, meanwhile adding small amounts of alkali as needed to neutralize the lactic acid formed through hydration of the anhydride. The solution is then made up to 1000 c.c. It may be sterilized in an autoclave and preserved in stoppered flasks or in sealed ampules.

Such molar solution may be obtained already prepared in 40 c.c. ampules (Eli Lilly and Company, Indianapolis.)

diluted by the addition of 5 volumes of sterile distilled water. A part of this (one third to one-half) is injected intravenously, to restore as quickly as possible diminished blood volume, while the remainder is administered subcutaneously or intraperitoneally, (3) administration of physiological buffer salts solution parenterally,* (4) the administration of dextrose solution to furnish fuel, to relieve ketosis and to help in re-establishing the glycogen reserves of the body. Dextrose solution in isotonic strength (6 per cent) may be given as such subcutaneously or mixed with equal parts of physiologic buffer salts solution. The dextrose may also to advantage be given by continuous slow intravenous injection. For this purpose a 10 per cent solution, either alone or mixed with an equal volume of physiologic buffer salts solution, is used. The rate of injection of the 10 per cent solution of dextrose should not exceed 3 c.c. per kilogram of body weight per hour. More rapid injection may result in glycosuria, edema, embarrassment of the circulation and at times to a general reaction with temperature elevation and chills. (5) The administration of citrated whole blood. This procedure should not be resorted to until after the fluid balance has been well restored, inasmuch as transfusions given in the presence of marked blood concentration may result in a still further increase in plasma protein content and an intensification of the phenomena of anhydremia.

After the fluid content of the blood has been restored, blood transfusion tends to reestablish the plasma protein level in the recipient when this is low as the result of poor nutrition or has been in part destroyed during the existence of anhydremia and is in consequence low when the blood volume has again been reestablished through the administration of fluid. Transfusion therefore tends to prevent the development of secondary nutritional edema. The administration of blood may furnish some bacterial antibodies, particularly to *B. coli*. Transfusion of whole blood also furnishes red blood cells, which are capable of functioning normally, and in this way tends to prevent the development of anemia after dehydration has been overcome.

The above measures designed particularly to restore normal blood and body fluid volume and chemical composition, can usually be carried out satisfactorily within the first twelve hours. Should severe diarrhea continue, the parenteral administration of physiologic buffer salts solution may have to be repeated two or three times daily, or given continuously by the slow intravenous drip method.

During the period of food restriction, which should last for twelve to forty eight hours or more, depending upon whether or not diarrhea

The physiological buffer salts solution (Hartmann's solution) has been described elsewhere.¹¹ It is essentially a mixture of Ringer's solution and sodium lactate and is designed to supply potassium, calcium and magnesium, in addition to sodium ions and chloride and enough potential bicarbonate to prevent the recurrence of acidosis, should diarrhea continue. This solution is obtainable in ampule form. (Eli Lilly and Company Indianapolis.)

tends to continue despite food restriction, it seems of value to offer small amounts of acidified and buffered water, which tends to keep the stomach and upper intestines sufficiently acid to prevent the growth of intestinal organisms. This buffered water is composed of lactic acid in 100 millimolar strength and sodium lactate in 50 millimolar strength.* It is sometimes advantageous to sweeten this mixture with saccharine.

After the preliminary starvation period, the most efficacious method of resuming feedings is to offer small amounts of Dryco (half-skimmed dried milk) or dried protein milk, diluted 1 to 10 with the above mentioned buffered mixture. Very gradually, after the condition of the patient improves and the diarrhea becomes less, the amount of food may be increased. We have found it satisfactory, first to concentrate somewhat the dried or protein milk dilution (making it 1 to 8) and then to add gradually the carbohydrate to the formula in the form of Kao syrup (dextrin and maltose). When roughly 6 per cent carbohydrate has been added to such a formula and the patient is taking amounts of such a formula normal for his age, evaporated milk diluted with an equal volume of buffered solution or 1 per cent lactic acid, and with the addition of 5 to 7 per cent of carbohydrate may be substituted for the protein milk mixture and in this way adequate calories may easily be given.

In general, the same measures found efficacious for the relief of dehydration and restoration of the normal chemical composition of the body fluids in the nondysenteric form of diarrhea were also found highly satisfactory in the more severe forms of acute bacillary dysentery. Because of the much greater frequency of severe ketosis in dysentery, dextrose seems more specifically indicated, and should be supplied in addition to physiologic buffer salts solution, at least as long as ketosis is present. The preliminary restriction of food has also been found efficacious. The feeding of buffered water, however, seems rarely necessary, because of the more normal secretion of gastric juice. In regard to dietary measures, the most important point would seem to be the restriction of fat during the period of toxemia. It is our impression that feeding of milk formulas containing 3 per cent fat or more tends to increase vomiting and to make the stools larger and more watery. After vomiting has ceased and the temperature has become normal or almost normal, it has been our plan to increase the food rapidly, so that an adequate amount of calories may be given. In order not to interfere with the healing of the ulcers in the intestinal mucous membrane, the food should contain little or no roughage. In addition to an adequate amount of milk with or without added carbo-

*This solution is prepared as follows

Lactic acid U S P	-----	15 c.c.
Sodium hydroxide 10 per cent	-----	20 c.c.
Water to	-----	100 c.c.

Before use the solution is diluted one part to ten with water

hydrate, such food substances as Jello fruit juices strained cereal arrowroot crackers with butter and jelly have been found useful

In any case in which parenteral infection is present whether as the primary cause of the diarrhea or as a secondary complication, such infection should receive appropriate treatment. The treatment of parenteral infections may include local treatment of the nose and throat, paracentesis of the ear drum or in those cases in which there is definite evidence of mastoid involvement, postauricular drainage or mastoid antrotomy. The latter procedure is rarely necessary except in the case of epidemic streptococcus infections. When such infections are present, and are the primary cause of the diarrhea, excellent results are obtained following antrotomy. When infections of the mastoid or of the nasal accessory sinuses are secondary manifestations, operative treatment may also be indicated but this is not followed by the same striking results as in the case of primary parenteral infections. After operation, the wounds heal slowly and the mortality is high. The diarrhea, not being dependent entirely upon the infection may be but little influenced. The purpose of treating the infections is to remove one of the complicating factors prejudicing recovery.

REFERENCES

1. Brown, Alan Tisdall, Frederick F., Wishart D F S Drake T G H, and Johnston, M M. *Southern M J* 13 107 1930
2. Johnston M. M., Brown Alan and Tisdall, F F. *Canadian M. A. J* 23 231, 1930
3. Johnston, M. M., Brown Alan and Kanke M J. *Am. J Dis. Child* 45 498 1923
4. Marriott, W M., and Davidson, L T. *Am. J Dis. Child.* 26 542 1928
5. Moro, E. *Jahrb f Kinderh.* 84 1 1916
6. Plantenga, B. B. B. *Jahrb f Kinderh.* 109 197 1925
7. Arnold, L. *Am J Dis Child.* 31 668 1920
8. Hartmann, A F., and Elman R. *J Exper Med.* 50 387, 1920
9. Hartmann, A F.: *Am J Dis Child.* 35 567 1928
10. Hartmann A F., and Senn Milton, J E. *J Clin Investigation* 11 337 1932
11. Hartmann, A F. *Colorado Med.* 26 2,3 1920

A NOTE ON THE PATHOGENESIS OF RENAL RICKETS

DERANGEMENTS OF CALCIUM AND PHOSPHORUS METABOLISM IN NEPHRITIS

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RENAL dwarfism and renal rickets are terms which have come to be commonly employed to designate the retarded growth, skeletal deformities and osteoporotic changes observed in children suffering from marked renal insufficiency. The association of late rickets with disease of the kidneys apparently was first noted by Lucas in 1883, and Fletcher in 1911 wrote the first clear description of a case of infantilism associated with chronic renal disease. That the condition is being increasingly recognized in recent years is attested by the many case reports and papers which have appeared, treating renal rickets as a disease entity, reviews of this extensive literature may be found in the papers of Barber (1921), Hunt (1927), Parsons (1927), Apert (1928), Mitchell (1930), Swart (1930), and Maddox (1932). While the symptomatology and pathology of the condition have been thoroughly described many times, the fundamental mechanism responsible for the bone changes remains obscure. The purpose of this paper is to present arguments in favor of an hypothesis which attempts to explain something of the derangement of mineral metabolism in chronic nephritis and to account for the faulty skeletal development. Part of the material presented herein was incorporated in an earlier review [Mitchell (1930)] of Nephrosclerosis in Childhood. Experimental studies along the lines indicated in this discussion are in progress and will be reported elsewhere in a later communication.

In renal rickets the general symptoms are those of chronic nephrosclerosis, namely, polydipsia, polyuria, retarded development, wasting, pallor and secondary anemia. Acute symptoms of uremia of varying degree occur and recur from time to time, especially coincidentally with various intercurrent infections. The renal insufficiency in these cases is usually a consequence of chronic sclerotic nephritis, of cystic disease of the kidneys, or of obstructive congenital anomalies of the urinary tract. In most instances in which renal efficiency was tested the function was found to be markedly reduced, often as low as 1 per cent of normal (dye excretion) and with inability to concentrate the urine. Skeletal changes varying in degree develop as a rule about the age of puberty. The age of onset of marked symptoms in most

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cases is from ten to fourteen years, but cases in younger children are seen not infrequently. The bones of these children display a picture of poor calcification and osteoporosis of varying severity. On the basis of the roentgenologic picture Parsons (1927) divided his cases into groups designated the "atrophic" type, the "florid" type and the "woolly, or stippled" type respectively, but these types appear to represent varying degrees of osteoporosis rather than real qualitative differences in their pathologic changes. The chemical changes in the blood are those ordinarily associated with severe chronic nephritis, that is, elevated nonprotein nitrogen, elevated inorganic phosphorus, lowered serum calcium, lowered bicarbonate and a tendency to acidosis. Explanation of the poor calcification of the bones in renal rickets

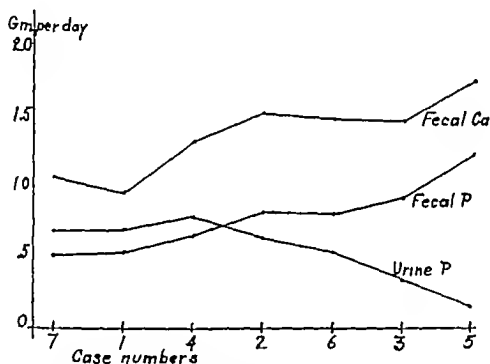


Fig. 1—Graphic representation of data taken from the studies of seven nephritic children reported by Boyd Courtney and MacLachlan (1925)

has been sought most often in the chemical changes of the blood, especially in the abnormal concentrations of calcium and phosphorus which are found in the blood serum.

Increased inorganic phosphorus in the blood in nephritis is generally stated to be due to inability of the kidneys to excrete the waste endogenous phosphates of the body but it must be recognized that the blood phosphorus level is not an index of the amount of phosphorus excretion or the lack of it and that an elevated blood phosphorus level is not a true measure of phosphorus retention. The real inability of diseased kidneys to excrete phosphorus can be more accurately evaluated if the efficiency of renal excretion of phosphorus is tested directly. Two studies may be cited in which such quantitative measurements have been made. Bolliger (1929) induced a form of slowly progressive sclerotic nephritis in dogs by exposing their kidneys to

high doses of roentgen rays. To test the renal efficiency for phosphorus excretion in these nephritic animals, he injected measured amounts of a buffered solution of sodium phosphate intravenously and determined the amount of phosphorus excreted in the urine during the succeeding two hours. During the slow evolution (thirty to ninety days) of renal sclerosis and loss of functioning kidney tissue which followed the irradiation of the kidneys, repeated tests showed a progressive decrease in the excretion of phosphates from around 80 per cent of the amount injected to a "trace." Tests with phenolsulphone phthalein in the same animals showed a parallel decrease in the excretion of the dye. Biam and Kay (1929) also devised a quantitative test of renal excretion of phosphates which they believed gave an index of renal function more significant than the usual dye excretion tests. In a series of normal persons and nephritic patients they determined the hourly rate of urinary phosphorus excretion immediately before and immediately after the injection of a measured amount of sodium glycerophosphate. In a group of patients with the diagnosis "chronic nephritis terminal stage" the urinary excretion of the injected phosphate was markedly reduced to between nothing and 30 per cent of that amount excreted by the normal control group.

In severe nephritis low serum calcium values have been found by Halverson, Mohler and Beigum (1917), Denis and Hobson (1923), de Wesselow (1923), Fetter (1923), Rabnowitch (1925), Schmitz, Rohdenburg and Myers (1926), Boyd, Courtney and MacLachlan (1926) and many others. Among these investigators there is general agreement that in nephritis the serum calcium exhibits roughly an inverse relationship to the inorganic phosphorus, that is, the serum calcium is usually low when the phosphorus is elevated. Experimental evidence that inorganic phosphorus has a strong influence upon the level at which calcium is carried in the blood is furnished by experiments such as those of Binger (1917) and of Tisdall (1922) wherein it was demonstrated that in dogs the intravenous injection of phosphoric acid and its sodium salts caused a marked depression of the serum calcium. Other factors, of course, play important rôles in governing the concentration of serum calcium, for example, a three-fold relationship of inorganic phosphorus, calcium and total protein of the blood serum has been defined by the studies of Peters and Eiserson (1929).

Laying stress upon the observations of low serum calcium values in renal rickets several investigators have attempted to explain the faulty bone calcification in this condition by citing the hypothesis of Howland and Kramer (1921) that undersaturation of the blood serum with calcium phosphate might account for the bone changes of infantile rickets. According to the supporters of this hypothesis, the depression of serum calcium by the elevated inorganic phosphorus found

in the blood in renal rickets may account for the failure of calcium to be deposited in the bones. The empiric $\text{Ca} \times \text{P}$ product as used by Howland and Kramer to indicate the total concentration of calcium phosphate in the plasma has been used by different writers both to support and to discount that contention. Parsons (1927) extended this argument by calculating $\text{Ca} \times \text{P}$ ion products for some of his own cases and others collected from the literature and attempted to show that the values for such ion products would be found to be in the range observed in infantile rickets if the dissociation constants reported by Holt LaMer and Chown (1925) were used taking into account the lowered serum P_{H} values observed in most of these cases. As an illustration of this he took data from a case in which Lathrop (1926) argued that the deformities were not true rickets because the $\text{Ca} \times \text{P}$ product was above the rachitic level. Lathrop's data recalculated with corrections for the very low serum P_{H} value recorded in the published article gave an ion product compatible with true rickets. Parsons however, took the single P_{H} determination (P_{H} 6.98) as characteristic of the reaction of this patient's blood while Lathrop's record indicates that this value was obtained at a time when this patient was in a state of acute acidosis verging on uremia. Certainly such a reaction could not have been characteristic of the blood of this patient in more normal periods.

The studies of Hastings Murray and Scudroy (1927) and others indicate that the theory of supersaturation of the blood plasma with calcium phosphate is inadequate to explain the processes of normal bone calcification. Even granting however the possible significance of serum $\text{Ca} \times \text{P}$ products in infantile rickets, it is probable that in renal rickets the $\text{Ca} \times \text{P}$ ion products will always except perhaps in the presence of severe acidosis be above what may be believed to indicate a significant reduction in the degree of saturation of the plasma with calcium phosphate. Since it seems unlikely that the actual concentration of either calcium or phosphorus in the circulating blood of patients with renal rickets is ever too low to permit calcium deposition in the tissues, it would appear that the defective bone development in this condition must be due to other underlying faults. Even in infantile rickets the blood chemical changes may be interpreted only as secondary manifestations of the disorder similar to the grossly visible bone changes, the more fundamental fault is a failure of absorption of calcium and phosphorus from the food in the intestine. With this in mind it seems worth while to consider here a few factors which are known to affect the total calcium and phosphorus metabolism of the body and especially the manner in which the absorption of calcium may be affected by certain conditions which develop in severe nephritis.

Phosphorus is one of the most important of those waste products which are, in health, ordinarily excreted by the kidneys. Normally in children the urinary phosphates represent about 50 per cent of the phosphorus intake, and, of the total output, about two-thirds leaves the body in the urine and about one-third in the feces. Many factors and events concomitant with nephritis, such as intercurrent infections, acidosis, etc., are known to increase cell catabolism and the liberation of phosphorus from the body in amounts more than normally excreted. What, then, must be the conditions in severe nephritis with poor renal function when those waste endogenous phosphates cannot leave the body by the usual route of the kidney? Even in the most marked states of nephritic acidosis the increased amount of phosphorus in the blood is too small to indicate an accumulation of the large amounts of phosphates which are ordinarily excreted in the urine.

Experimental studies of calcium and phosphorus metabolism furnish evidence that the intestine has the ability to secrete both calcium and phosphorus in considerable amounts [Beigem (1926)]. In the few published studies of calcium and phosphorus metabolism in nephritic children that are available, evidence also may be found that in nephritis with impaired renal function the intestinal secretion of phosphorus may be increased by the waste endogenous phosphates escaping from the body through this route. That the increase of intestinal phosphates by such a change in the route of phosphorus excretion may indirectly have a deleterious effect can be surmised from the fact that these waste phosphates are in forms well suited for precipitating calcium in the intestinal tract. As will be noted in the succeeding paragraphs, even under normal conditions if the concentration of phosphates in the intestine is greatly increased by a high phosphorus intake in the diet the absorption of calcium is interfered with, presumably by the formation of insoluble calcium phosphates. If the intestinal contents have added to them those waste endogenous phosphates which ordinarily leave the body in the urine, a similar effect of diminished calcium absorption may well be expected. Should the excreted intestinal phosphates be in sufficient amount to interfere considerably with calcium absorption, it should also be expected that continued calcium deprivation will result in general systemic manifestations of a lack of calcium in the body. The argument that a disturbance of calcium metabolism of such a nature can occur and can account for the poor skeletal development seen in renal rickets is supported by various observations cited in the following paragraphs.

Experimentally, rickets is easily produced in rats (in the absence of ultraviolet light or vitamin D) by diets which have either a high calcium and low phosphorus content or a low calcium and high phosphorus content. A high calcium, low phosphorus diet induces rickets in rats which is characterized by chemical changes in the blood similar to those found in human infantile rickets, namely, normal serum

calcium and low inorganic phosphorus. On the other hand, a low calcium, high phosphorus diet induces rickets characterized by low serum calcium and high inorganic phosphorus. Food metabolism studies done on such experimental animals make it apparent that a relative excess of either calcium or phosphorus in the diet will interfere with the absorption of the other from the intestine, by the formation of insoluble calcium phosphates which, unabsorbed, leave the body in the feces. It may be noted here that Shipley, Park, McCollum and Summonds, in 1922, in a paper entitled 'Is There More Than One Kind of Rickets?' discussed these two types of experimental rickets in relation to certain forms of rickets observed clinically and described a case of renal rickets in which they thought the changes resembled those of the 'low calcium' type of rickets which they had induced in rats by the low calcium diet.

In agreement with such observations in experimental animals there have been reported a few studies in normal human infants which indicate that here too an excessive intake of either calcium or phosphorus may interfere with the absorption of the other element from the intestine. Of such studies, those of Orr, Holt, Wilkins and Boone (1934) are probably the clearest. They observed two infants during three metabolism periods of four days each with intervals of rest between, giving in the successive periods a normal diet, a high calcium diet and a high phosphorus diet. With the high calcium diet more calcium was retained, the serum calcium rose where it had been low and more calcium was excreted in the urine. Phosphorus retention was diminished; considerable amounts of phosphorus were diverted from the urine to the stools and the serum phosphorus was lowered. With the high phosphorus diet there was no increase in the phosphorus retention and in one case the phosphorus retention diminished. The calcium retention was markedly decreased with a great increase in the fecal calcium and decrease of the urinary calcium. In one case there was a definite fall in the serum calcium.

The studies of Boyd, Courtney and MacLachlan (1926) of calcium and phosphorus metabolism in nephritis furnish data which indicate that there was a changed route of phosphorus excretion in a group of nephritic children who seemingly had comparatively mild renal impairment. In their group of fifteen children with nephritis of various types, the first seven cases were described as having no edema and having a tendency to elevation of the phosphorus and depression of the calcium in the blood serum, changes comparable to those found in patients with renal rickets. The data from these seven cases are presented graphically in Fig. 1 arranged in the order of increasing daily fecal phosphorus excretion and of decreasing urinary phosphorus excretion. Arranged thus without regard to other factors, it may be seen that there was roughly a reciprocal relationship between the amounts of phosphorus excreted in the urine and in the feces, and

that as the phosphorus excretion was greater in the feces the increasing amounts of calcium lost in the feces were about proportional to the increasing fecal phosphorus

In a study of calcium and phosphorus metabolism in a group of eleven nephritic children Ford (1931) found a similar deviation in the excretion of phosphorus from the urine to the feces, with losses of calcium in the feces closely parallel to the fecal excretion of phosphorus. For comparison, Ford collected from several sources in the literature the data on calcium and phosphorus metabolism studies of twenty-two normal children. In this group the fecal phosphorus amounted to 30.3 per cent of the intake and 39.2 per cent of the total output, the fecal calcium excretion was 64.7 per cent of the intake or 91 per cent of the total output. In Ford's group of eleven nephritic children (various diagnoses, and of varying severity of the nephritis) the fecal phosphorus was 54.2 per cent of the intake or 62.3 per cent of the total output, while the fecal calcium excretion was 78 per cent of the intake or 97.4 per cent of the total output. "Thus, an increase, relative and absolute, is found in both the calcium and phosphorus contents of the feces, of which the increase in phosphorus is relatively the greater."

Data from mineral balance studies of three nephritic children, which were made available through the kindness of Dr. L. Schoenthal in a personal communication, also give evidence of an increased excretion of phosphorus in the feces. These figures were published in the review of nephrosclerosis previously cited [Mitchell (1930)]. During the period of study, in Schoenthal's patients the fecal phosphorus represented respectively 50 per cent, 65 per cent and 75 per cent of the total phosphorus output. In two of the children there was a negative phosphorus balance with the fecal phosphorus amounting respectively to 90.6 per cent and 112.9 per cent of the phosphorus intake. The child in whom the fecal phosphorus was actually in excess of the phosphorus intake during the period of study, was suffering from renal rickets, the case reported by Schoenthal and Burpee (1930).

As previously stated, many circumstances commonly arising in nephritis tend to increase cell catabolism and to liberate phosphorus from the body in amounts greater than normally excreted, and with poor renal function, all such factors make it more difficult for the nephritic child to maintain normal calcium and phosphorus metabolism. The intoxications of bacterial infections increase cell catabolism, and the nephritic is frequently thrown into mild or severe acidosis by various intercurrent infections which would be of slight significance to the person with normal kidneys. In subjects with normal renal function, states of acidosis induced in many ways are attended with marked phosphaturia. Carbon dioxide acidosis induced by rebreathing and the lactic acid acidosis of muscular exercise

[Harvard and Reay (1926)], acidosis induced by the ingestion of ammonium chloride or other acid substances [Haldane, Hill and Luck (1923) and Morris (1930)] ketosis induced by a high fat low carbohydrate diet [Nelson (1928)] diabetic acidosis [von Noorden (1907)] Haldane Wigglesworth and Woodrow (1924) and Kay (1924) showed that in ammonium chloride acidosis the labile organic acid soluble phosphorus—the so called ester phosphorus fraction—in the blood cells was markedly reduced and presumably was the source of a considerable part of the increased phosphate lost in the urine. The mechanism by which the phosphates are released from the body in response to acidosis is not clear but it is significant that certain of the labile organic phosphorus compounds in the cells of the body tend to split readily to yield inorganic phosphorus when the reaction of their surrounding fluids is changed even slightly toward increased acidity [Martland (1925)]. In some studies of the behavior of phosphorus during glycolysis in blood taken from nephritic patients in severe states of acidosis, hydrolysis of the organic acid soluble phosphorus of the blood cells with liberation of inorganic phosphorus has been observed to occur much more rapidly than in normal blood [Guest (1932)]. In the nephritic patient with marked renal insufficiency each of these various circumstances which results in increased liberation of phosphorus from the body may impose a further handicap upon the absorption of calcium if the extra phosphates are excreted into the bowel. Parsons (1927) and others point out that in states of acidosis there is also an increased mobilization of calcium stored in the bones. Repeated transitory disturbances such as these can easily account for the picture of 'flux between healing and relapse' which Shipley, Park, McCollum and Simmonds (1922) described as characteristic of the bone changes in renal rickets.

Examples may be cited of substances other than phosphorus which interfere with absorption of calcium from the intestine, with consequent deleterious effects of calcium deprivation. It has been shown that high fat intake or poor utilization of fats and fatty acids results in the formation of insoluble calcium soaps in the intestine and in increased output of calcium in the feces [Lindberg (1917) Givens (1917) Sawyer Baumann and Stevens (1918) Holt Courtney and Fales (1920) and Telfer (1926)]. Such losses of calcium can account for the low calcium type of rickets and osteoporotic changes commonly observed in celiac disease as well as in other forms of chronic steatorrhea. Parsons (1927) has described the gross similarities in the bone changes of renal rickets and celiac rickets.

SUMMARY

In types of nephritis characterized by relative inability of the kidneys to excrete phosphates there exists a considerable amount of evidence that the waste endogenous phosphates of the body which are

ordinarily found in the urine may be excreted through the bowel, and that the phosphates thereby increased in the intestinal contents can interfere with the absorption of calcium by the formation of insoluble calcium phosphates which, unabsorbed, leave the body in the feces. It is suggested that long-continued partial starvation of calcium resulting from this metabolic fault is principally responsible for the condition known as renal rickets, that is, the low calcium type of rickets seen accompanying marked renal insufficiency in growing children.

REFERENCES

- Apert, E. *Presse méd* 36 577, 1928
 Barber, H. *Quart J Med* 14 205, 1921
 Bergeim, O. *J Biol Chem* 70 29, 35, 47 and 51, 1926
 Binger, C. *J Pharmacol & Exper Therap* 10 105, 1917
 Bolliger, A. *M J Australia* 1 650, 1929
 Boyd, G. L., Courtney, A. M., and MacLachlan, I. F. *Am J Dis Child* 32 29, 1926
 Brain, R. T., and Kay, H. D. *Quart J Med* 22 203, 1929
 Denis, W., and Hobson, S. *J Biol Chem* 55 183, 1923
 De Wesselow, O. L. V. *Quart J Med* 16 341, 1923
 Fetter, W. J. *Arch Int. Med* 31 413, 1923
 Fletcher, M. *Proc Roy Soc Med (Sec Dis. Child)* 4 95, 1911
 Ford, F. J. *Arch Dis Childhood* 6 209, 1931
 Givens, M. H. *J Biol. Chem* 31 435, 1917
 Gnest, G. M. *J Clin Investigation* 11 555, 571, 1932
 Haldane, J. B. S., Hill, R., and Luck, J. M. *J Physiol* 57 301, 1923
 Haldane, J. B. S., Wigglesworth, V. B., and Woodrow, C. E. *Proc. Roy Soc.* 96, Series B 15, 1924
 Halverson, J. O., Mohler, H. K., and Bergeim, O. *J Biol Chem* 32 171, 1917
 Hastings, A. B., Murray, C. D., and Sendroy, J. *J Biol Chem* 71 723, 783 and 797, 1927
 Havard, R. E., and Reay, G. A. *J Physiol* 61 35, 1926
 Holt, L. E., Courtney, A. M., and Fales, H. L. *Am J Dis Child* 19 97, 1920
 Holt, L. E., Jr., La Mer, V. K., and Chown, H. B. *J Biol Chem.* 64 509, 567 and 579, 1925
 Howland, J., and Kramer, B. *Am J Dis Child.* 22 105, 1921, *Monatschr f Kinderh* 25 279, 1923. See also Howland, J. *Medicine* 2 349, 1923, and Shipley, P. G., Kramer, B., and Howland, J. *Am J Dis Child.* 30 37, 1925
 Hunt, F. C. *Am J Dis Child* 34 234, 1927
 Kay, H. D. *Biochem. J* 18 1133, 1924
 Lathrop, F. W. *Arch Int Med* 38 612, 1926
 Lindberg, G. *Ztschr f Kinderh* 16 90, 1917
 Lucas, R. C. *Lancet* 1 993, 1883
 Maddox, K. *M. J Australia* 1 487, 1932
 Martland, M. *Biochem J* 19 117, 1925
 Mitchell, A. G. *Am J Dis Child* 40 101, 1930
 Morris, N., and MacRae, O. *Arch Dis Childhood* 5 207, 1930
 Nelson, M. V. *Am J Dis Child* 36 716, 1928
 Orr, W. J., Holt, L. E., Jr., Wilkins, L., and Boone, F. H. *Am J Dis Child* 28 574, 1924
 Parsons, L. G. *Arch Dis Childhood* 2 1, 1927
 Peters, J. P., and Emerson, L. *J Biol Chem* 84 155, 1929
 Rabinowitch, L. M. *J Biol Chem* 62 667, 1925
 Sawyer, M., Baumann, L., and Stevens, F. A. *J Biol Chem* 33 103, 1918
 Schmitz, H. W., Rohdenburg, E. L., and Myers, V. *Arch Int Med* 37 233, 1926
 Schoenthal, L., and Burpee, C. *Am J Dis Child* 39 517, 1930
 Swart, H. A. *J Bone and Joint Surg* 12 876, 1930
 Telfer, S. V. *Quart J Med* 20 1, 1926
 Tisdall, F. F. *J Biol Chem* 54 35, 1922
 Von Noorden, C. *Metabolism and Practical Medicine*, Chicago, Keener & Co., 1907, vol. 2

THE ALLEGED CORRELATION BETWEEN THE RATE OF GROWTH OF THE SUCKLING AND THE COMPOSITION OF THE MILK OF THE SPECIES

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DURING the last quarter of the Nineteenth Century Professor Bunge¹ of Basel and his pupils Pröschner² and Abderhalden³ became greatly interested in a relationship between the composition of milk, the composition of the body of the suckling and its rate of growth. Attention was also called to the observation that as the suckling grows the composition of its tissues changes and that a corresponding change occurs in the milk supplied by the mother. The chemical analyses and correlations had to do principally with protein and the inorganic constituents, particularly calcium and phosphorus.

In respect to the relationship of the analyses of milk to those of the body of the suckling the summary by Abderhalden³ is as follows: "Except as regards the composition of the human infant and human milk, we find by a comparison of the corresponding values that there is a striking agreement between the ash of the young animal and that of the milk. In the case of human beings, however, we do not find any such agreement. Bunge explains this fact by the assumption that the ash content of milk has not only the task of building up tissue but also serves in the preparation of the excreta especially the urine. The more rapid the growth of the suckling the less apparent will be the influence of the latter function. It is, therefore, in general not to be expected that the percentage of composition of the milk of the infant will agree so closely in the case of human beings as with animals such as dogs, rabbits, and guinea pigs, which require the mother's milk for but a short time after birth but are soon placed upon a diet of green fodder. It is easy to see that a milk corresponding closely to the chemical composition of the young as regards the inorganic constituents will be more suitable for animals which develop very rapidly, whereas with the species which develop more slowly the building up of the separate tissues does not take place so uniformly and there are not so many changes taking place at the time when the growing organism changes to another source of nourishment." (p. 369)

The alleged correlation between the composition of milk in respect to protein, ash, calcium and phosphorus and the rate of growth of the suckling is shown in a table by Abderhalden³ (Table I)

From the Department of Pediatrics, Yale University School of Medicine. Presented in abstract before The American Pediatric Society Thirty-eighth Annual Meeting 1926.

TABLE I
THE ABDEHILDEN TABLE

SPECIES	DAYS REQUIRED TO DOUBLE BIRTH WEIGHT	100 PARTS BY WEIGHT OF MILK CONTAIN			
		ALBUMIN	ASH	LIME	PHOSPHORIC ACID
Man	180	1 6	0 2	0 0328	0 0473
Horse	60	2 0	0 4	0 124	0 131
Cow	47	3 5	0 7	0 160	0 197
Goat	22	3 67	0 7713	0 1974	0 2840
Sheep	15	4 88	0 8406	0 2453	0 2928
Pig	14	5 21	0 8071	0 2489	0 3078
Cat	9½	7 00	1 02	—	—
Dog	9	7 44	1 3282	0 4545	0 5078
Rabbit	6	10 38	2 4998	0 8914	0 9967

On this table Abderhalden comments as follows ⁸ "It is to be assumed *a priori* that an animal which develops rapidly will require more building material than one whose development is slower. If we compare the time required by the suckling to double its weight at birth with the amounts of albumin and ash—perhaps the most essential constituents for the formation of the tissues—contained in 100 parts of milk, it is evident at a glance that the amount of these increases in proportion as the development of the animal is rapid" (p 404) "The fact that the milk of different species of animals varies greatly is of much significance. The composition of the milk evidently has an effect upon the rate of development of the suckling. It is natural to expect that the richer the milk is in its organic and inorganic constituents, the more rapidly the suckling is able to build up its tissues. If the milk of different species of animals all had the same composition, then the desired effect could be produced only by means of a much greater production of milk, and similarly a correspondingly greater quantity would have to be taken into the system of the suckling" (p 655)

That all biologists did not interpret these interesting data as Abderhalden did is shown by the following quotation from Professor C S Minot's book on "The Problem of Age, Growth and Death"¹⁰ "This looks at first sight as if there were a relation between the composition of the milk and the period of growth of the animal, but you know very well that if you take the milk of a cow, which is very much richer in proteid material, and feed it to a baby, a human baby, that baby does not grow at the same rate as the young cow, but grows at the human rate. It is obvious, therefore, that it is somewhat more complicated than a mere question of food supply. We have here in fact one of the beautiful illustrations of the teleological mechanism of the body. These various species have then characteristic rates of growth, and by an exquisite adaptation, the composition of the mother's milk has become such that it supplies the young of the species each with the proper quantum of

protein material which is needed for the rate of growth that the young offspring is capable of. It is a beautiful adjustment but there is not a causal relation between the proteid matter of the mother's milk and the rate of growth of the young. It is an example of correlation not of causation.

The Abderhalden Table is reproduced with varying degrees of consideration in many standard treatises dealing from one approach or another, with nutrition. One may cite as examples the textbooks of Czerny and Keller¹⁰ Finkelstein¹¹ Pfundler and Schlossmann¹ Henbaer,¹² Langstein and Nassau¹⁴ Lusk¹³ Sherman¹⁶ Starling¹⁷ Hammarsten,¹⁸ and Marfan.¹

As the result of a study by the author in 1925 entitled *Comparison and Interpretation on a Calorie Basis of the Milk Mixtures Used in Infant Feeding*,¹⁹ it seemed pertinent to apply the same method of evaluation to the data of the Bunge Abderhalden Pröschel investigations. A few quotations from this paper will give background and the method of study. The formulas of the food mixtures used in infant feeding are ordinarily expressed as the proportions by weight or volume which the various food components are of the total mass of the food—the so called percentage system. So formulated certain similarities and differences in foods may be suggested in a vague way but the essential fact inherent in the percentage system namely that the values of the nutrients are ratios which express only degree of concentration is often lost sight of. For comparative purposes especially, it is difficult to perceive significant facts from small often fractional, percentage values of protein carbohydrate and fat which shift with changes in volume. More helpful data would be apparent if water were disregarded and the food constituents were expressed as proportions of the solids in the mixture. Protein, carbohydrate, fat and salts would then be shown as they are related to each other independent of their relation to the diluent.

Although it is possible to establish a satisfactory means of comparative study of various foods on a quantitative basis it is advisable to go further to a more fundamental unit for a common currency in infant feeding. The calorie is the unit used everywhere by physiologists in the investigation of problems of nutrition. Itself a measure of energy the calorie is used constantly in metabolism studies. As a physiologic unit, the calorie is greatly superior to the gram as the unit to which the protein carbohydrate and fat food components may be reduced. The calorie is a least common denominator of all energy yielding food constituents and their derivatives. Briefly stated, in the analyses and comparisons of milk mixtures described in this paper the total calorie value of a given amount of the food as fed is estimated and the percentage relationships which exist between the total calories and the

calories of protein, of carbohydrate and of fat are then determined. Thus, the energy-yielding components are expressed and compared without confusing alliances with volumetric data."

"In regard to the salt content of infant feeding mixtures, it may be stated that in general the mineral constituents of most of them parallel the milk content. When milk is diluted with water and the requisite calories of a milk mixture are made up with salt-poor food components, the actual mineral intake is greatly reduced. The salt content of milk mixtures may be so expressed to bring out its relationship to the total energy value of the food or to that of any one of the food components." For example, in human milk—on the basis that 100 cc contain 200 mg of inorganic salts and have an energy value of 64 calories of which 4.6 are supplied by protein—there are 3.1 mg of ash for every calorie of milk and 43 mg for every calorie of protein. The individual electrolytes may be similarly treated.

DATA

In Table II A I have added to the Abderhalden Table (leaving out the data on calcium and phosphorus) the figures for lactose and fat which were given in the original analyses on which the table was based 2, 3, 4, 5, 6. Then in Table II B, I have set down computations of the calories per 100 cc of milk, the percentage of these calories in protein, carbohydrate and fat and the milligrams of ash per calorie of milk. These data are graphically shown on Chart 1.

In Table III I have set down data corresponding to those set forth in Table II but concerned only with milks used in human dietary in one country or another.* These data are shown graphically in Chart 2. Similarly, in Table IV, are set forth data concerning the milks of animals rarely studied. It should be pointed out that in Tables I, II and IV there are analyses of milks which because of the inherent difficulties in sampling may well be inaccurate as indicative of the composition of the average mature milk of the species. It was for this reason that Table III was developed with the thought that the analyses there given were concerned with milks more or less extensively used in certain localities and samples were, therefore, available which are truly representative of the mature milk of the species.

In Table V are data showing the rate of growth of the female young of various breeds of dairy cattle and the composition of the milks of the breeds. In addition, the calories per 100 cc of milk have been computed and also the percentage of these calories in protein, lactose and fat.

The studies of the ash of various milks are set forth in Tables VI, VII and VIII. In Table VI, the Bunge Abderhalden-Proschner data are set forth in respect to the milligrams of ash per calorie of milk and per calorie of protein, also the relation of "lime" and "phosphoric acid" to calories of protein. In Table VII are set forth for those milks enumerated in Table III, the relationship of total ash and of six of the most important constituents, quantitatively speaking, to calories of milk. Table VIII gives the data with respect to the same milks of the relationships of the total ash and of the same six constituents of the ash to calories of protein.

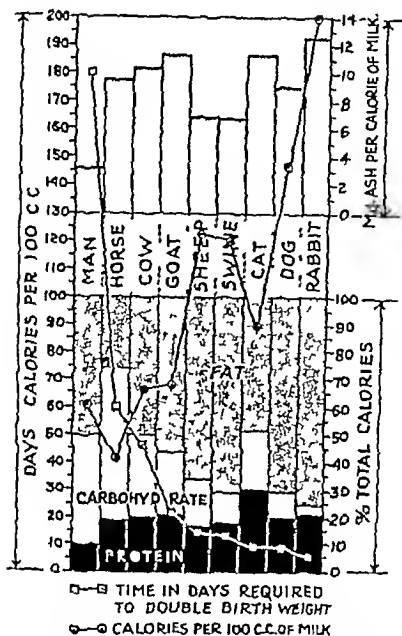


Chart 1—Based on data in Table II. Graphs show caloric value per 100 c.c. of milk of species shown in Abderhalden Table and percentage of calories in protein carbohydrate and fat also, milligrams of ash per calorie and days required by sucklings to double birth weight.

TABLE II

THE ABDERHALDEN TABLE WITH ADDITIONAL DATA AND COMPUTATIONS

A						B				
SPECIES	DAYS RE QUIRED TO DOUBLE BIRTH WEIGHT	PER CENT OF SOLIDS IN				CAL- ORIES PER 100 CC.	PER CENT OF TOTAL CALORIES IN			MG ASH PER CALORIE OF MILK
		PROT	CARB.	FAT	ASH		PROT	CARB.	FAT	
Man	180	16	61	34	020	61	10	40	50	8.2
Horse	00	20	57	12	040	42	10	55	26	9.5
Cow	47	25	49	27	070	67	20	30	50	10.4
Goat	23	367	561	4.33	077	68	31	22	57	11.3
Sheep	15	4.88	5.04	9.29	084	123	17	17	66	6.3
Pig	14	5.21	8.3	9.54	080	120	18	11	71	6.7
Cat	9½	7.00	4.78	4.75	1.02	80	30	22	48	11.3
Dog	9	7.44	3.84	11.62	1.32	147	20	9	71	9.0
Rabbit	6	10.38	1.98	16.71	2.49	200	21	4	75	12.5

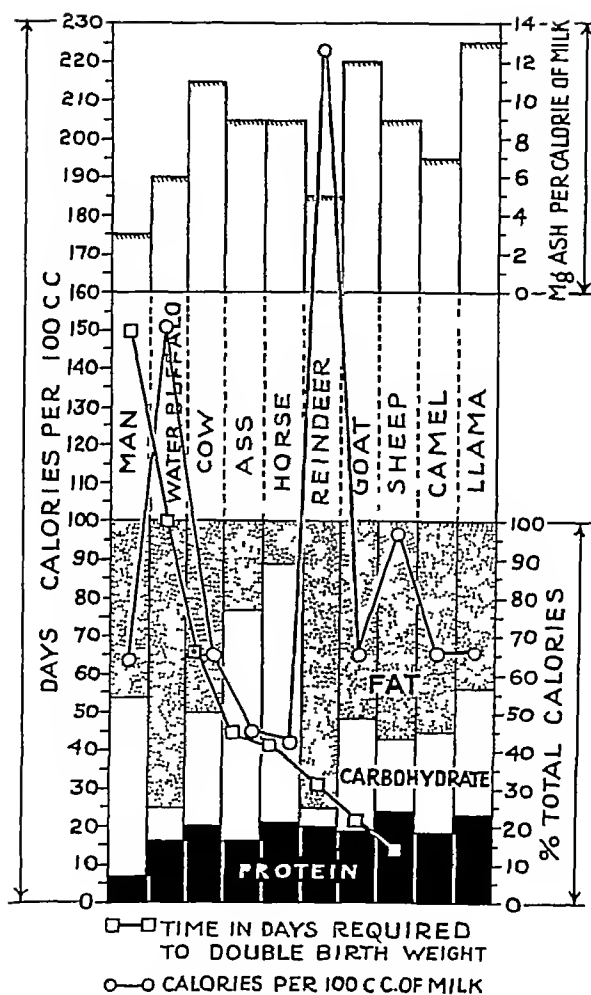


Chart 2—Based on data in Table III. Graphs show caloric value per 100 c.c. of milk used in human dietary and percentage of calories in protein carbohydrate and fat also milligrams of ash per calorie and days required by sucklings to double birth weight.

TABLE III

A NEW TABLE BASED ON DATA FROM THE LITERATURE AND FROM PERSONAL COMMUNICATIONS. THESE DATA HAVE TO DO ONLY WITH MILKS USED IN INFANT FEEDING

SPECIES	DAYS REQUIRED TO DOUBLE BIRTH WEIGHT	PER CENT OF SOLIDS IN				CALORIES PER 100 C.C.	PER CENT OF TOTAL CALORIES IN			MG ASH PER CALORIE OF MILK
		PROT	CARB	FAT	ASH		PROT	CARB	FAT	
Man	150	11.5	7.5	3.26	0.2	64	7	47	46	3
Water Buffalo	100	6.03	3.74	12.46	0.89	151	16	9	75	6
Cow	66.76	3.28	4.84	3.61	0.72	65	20	30	50	11
Ass	45.60	1.82	6.86	1.13	0.42	45	16	61	23	9
Horse	42	2.2	6.97	0.54	0.41	42	21	68	11	9
Reindeer	31	11.1	2.7	18.7	1.2	223	20	5	75	5
Goat	22	3.18	4.62	3.79	0.79	65	19	29	52	12
Sheep	14	5.83	4.72	6.12	0.89	97	24	19	57	9
Camel	?	2.92	4.58	4.1	0.5	66	18	27	55	7
Llama	?	3.9	5.6	3.15	0.8	66	23	34	43	13

TABLE IV
ANOTHER TABLE BASED ON DATA LESS ACCEPTABLE, FOR THE MOST PART, THAN THOSE USED FOR TABLE III

SPECIES	DAYS REQUIRED TO DOUBLE BIRTH WEIGHT	PER CENT OF SOLIDS IN				CALORIES PER 100 G.	PER CENT OF TOTAL CALORIES IN			NO ABS PER CALORIE OF MILK	NO ABS PER CALORIE OF PROTEIN
		PROT	CARD.	FAT	ASH		PROT	CARD.	FAT		
Guinea Pig	12-14	5.0 at	16 at	7.1 at	0.77	93	22	0	89	8.0	38
Pig	7-10	0.08	5.21	6.68	1.0	105	22	20	58	0.0	40
Elephants	?	8.40	7.18	20.58	0.63	22.7	0	33	81	2.8	47
Elephants	?	2.51	8.59	9.10	0.5	156	8	27	60	4.0	70
Elephant	?	3.21	7.39	22.07	0.63	241	5	33	82	0.0	40
Zebu	?	3.03	5.34	4.8	0.7	17	16	27	51	0.0	38
Blue Whale	?	13.42	5.63	20.0	1.48	202	20	10	70	7	30
Bartenwhale	?	9.43	0.39	19.4	0.90	212	19	-	82	4.6	20
Monkey (Mangabey)	?	2.8	7.0	11	0.1	50	18	1	21	2.0	10
Fox	5	6.2	4.50	6.3	0.96	100	17	18	57	0.0	38

TABLE V

DATA CONCERNING THE COMPOSITION OF MILK AND RATE OF GROWTH OF VARIOUS BREEDS OF DAIRY COW

BREED OF COW	DAYS REQUIRED TO DOUBLE BIRTH WEIGHT	PER CENT OF SOLIDS IN				CALORIES PER 100 C C OF MILK	PER CENT OF TOTAL CALORIES IN		
		PROT	CARB	FAT	ASH		PROT	CARB	FAT
Holstein	76	3.1	4.6	3.4	0.68	62	20	30	50
Shorthorn	73	3.3	4.8	3.6	0.73	65	20	30	50
Ayrshire	69	3.3	5.0	3.8	0.69	68	20	29	51
Jersey	66	3.8	5.0	5.1	0.75	81	18	25	57
Guernsey	—	3.8	4.9	4.9	0.75	80	20	25	55

TABLE VI

THE RELATIONSHIP OF TOTAL ASH TO CALORIES OF MILK AND OF TOTAL ASH, "LIME" AND "PHOSPHORIC ACID" TO CALORIES OF PROTEIN ACCORDING TO BUNOE PROSCHEER ABERHALDEN DATA

SPECIES	CAL. PER 100 C C OF MILK	MG ASH PER CALORIE OF MILK	CAL OF PROTEIN PER 100 C C OF MILK	MG OF ASH PER CALORIE OF PROTEIN	MG OF LIME PER CALORIE OF PROTEIN	MG OF PHOS ACID PER CALORIE OF PROTEIN
Man	61	3.2	6.4	33	5	7
Horse	42	9.5	8.0	50	15	16
Cow	67	10.4	14.0	50	11	14
Goat	68	11.3	14.68	51	13	19
Sheep	123	6.8	19.52	42	13	15
Pig	120	6.7	20.84	38	12	14
Cat	90	11.3	28.0	36	—	—
Dog	147	9.0	29.76	44	15	17
Rabbit	200	12.5	41.52	60	21	24

TABLE VII

THE RELATIONSHIP OF THE TOTAL ASH AND SOME OF ITS CONSTITUENT ELECTROLYTES TO CALORIES OF THOSE MILKS TABULATED IN TABLE III

SPECIES	CAL PER 100 C C OF MILK	MG PER CALORIE OF MILK OF						
		TOTAL ASH	K ₂ O	Na ₂ O	CaO	MgO	P ₂ O ₅	CL
Man	64	3	0.95	0.20	0.72	0.11	0.54	0.56
Water Buffalo	151	6	0.86	0.36	2.0	0.18	2.0	0.44
Cow	65	11	2.75	0.78	2.6	0.31	2.92	1.52
Ass	45	9	2.3	0.38	2.89	0.20	2.65	1.09
Horse	42	9	2.45	0.33	2.93	0.29	3.1	0.73
Reindeer	223	5	0.79	0.87	1.36	0.14	1.64	0.22
Goat	65	12	2.0	0.95	3.03	0.24	4.37	1.55
Sheep	97	9	2.22	0.40	2.85	0.13	2.77	0.7
Camel	66	7	1.4	0.27	2.04	0.21	2.29	1.16

ANALYSIS OF DATA

Despite possible inaccuracies in certain data there is one finding of striking constancy in the analyses as tabulated, namely, most milks have about 20 per cent of the total calories in protein. There are exceptions but the only one which is certain is human milk which has less than 10 per cent of its total calories in protein. It would seem from Table IV that in this respect the milk of the elephant is very much like human

TABLE VIII

THE RELATIONSHIP OF THE TOTAL ASH AND SOME OF ITS CONSTITUENT ELECTROLYTES TO CALORIES OF PROTEIN OF THOSE MILKS TABULATED IN TABLE III

SPECIES	CAL. OF PROTEIN PER 100 C.C. OF MILK	MG PER CALORIE OF PROTEIN OF						
		TOTAL ASH	K ₂ O	Na ₂ O	CaO	MgO	P ₂ O ₅	CL
Man	4.00	43	13.4	2.8	0.0	1.6	7.5	7.0
Water Buffalo	24.12	37	5.4	2.3	12.5	1.0	12.4	2.7
Cow	13.12	55	13.6	3.0	12.0	1.5	14.5	7.4
Ass	7.29	59	14.0	2.3	17.8	1.2	16.3	0.7
Horse	8.8	46	11.7	1.0	14.0	1.4	14.9	3.5
Reindeer	44.4	27	3.0	4.4	0.8	0.73	8.2	1.1
Goat	12.72	60	10.2	4.9	15.5	1.2	22.0	8.0
Sheep	23.32	38	0.3	1.69	11.9	0.55	11.6	2.0
Camel	11.68	43	7.0	1.5	11.5	2.1	12.9	6.1

The sources of the data on which Tables III, IV, V, VI and VII are based will be found following the summary.

milk. In this Table I have set forth three analyses of elephant's milk although there are variations, chiefly in the amounts of fat, nevertheless the percentage of total calories in protein in all three calculations is between ten. The striking fact remains that in analyses the essential accuracy of which in all respects one has little reason to question human milk stands apart from that of all other species examined in respect to the percentage of total calories in protein.

Out of these observations comes another namely that there is no correlation between the rate of growth of the suckling and the protein-calorie relationship. Indeed if there is any correlation in this domain at all it is closer between rapidity of growth and the calorie concentration of the whole milk than between any other two variables in the data. But this correlation while suggestively close in Table II and Chart 1 is vitiated when one studies the data in Table III and Chart 2. For example the reindeer calf doubles its birth weight in one third the time required by the water buffalo calf, but the mother of each suckling supplies milk of very high calorie value.

In all of these matters the factors of maturity of the suckling, total calorie requirement and quantity of milk taken per diem must be kept in mind. Climate seems to play no rôle when one observes, in the example of the reindeer and water buffalo just cited that one animal is arctic in its habitat and the other tropical. Within the species itself there are considerable variations in composition of milk and in rapidity of growth. One has but to observe the variations in the composition of the milk of different breeds of dairy cows and the different rates of which the female calves of such cows grow (Table V).

One might also call attention to the type of body covering of the different animals under consideration. In some the skin is bare, in others covered by hair and in others, by wool. The cystine content of

some samples of hair is high, but the milks showing a high percentage of the total calories in protein are those in which, for the most part, casein is the predominant milk protein and casein is low in cystine.*

Apparently there is no correlation between the protein-total calorie relationship and the quality of the protein so far as albumin and casein content is concerned. In the milks of the species listed in Table III (no data for llama) casein is greatly in excess of albumin excepting in that of man and ass²⁵

It would be of great biological interest if a study of the milks of the various primates could be made along the lines here suggested. If some of the milks showed the protein total calorie configuration characteristic of human milk, while others showed the pattern so characteristic of all the other milks here studied, the matter might have phylogenetic significance. In Table IV I have given the only analysis of the milk of a primate (Mangabey) of which I have knowledge. Eighteen per cent of the calories are in protein.

When one turns from a consideration of protein to that of the relation of the ash and of its individual constituents to the total calories (Tables VI and VII) one finds little correlation of these data with rate of growth. If the ash is expressed as milligrams per calorie of milk, the ash of human milk is lower than that of any other of the animals studied. If one expresses the total ash as milligrams per calorie of protein (Tables VI and VIII), there is, perhaps, less extreme variation. If one excepts the data concerning reindeer milk, the range of variation between the lowest (37) and highest (60) values is 23, this, of course, does not approach so nearly a constant in the ash-calorie correlation as is indicated above to be true of the protein-calorie relationship. If one studies the ash-calorie relationship of each of the individual electrolytes of the total ash (Tables VI, VII and VIII), no constancy for the values for each species in relation either to calories of milk or to calories of protein is obvious. In general, one would expect and does find a more constant correlation between ash and protein calories than between ash and total milk calories. It is possible, however, that the electrolytes are more closely related to protein itself than to nutritional requirements.

*The body coverings of the animals discussed in this paper are a matter of common knowledge with the possible exception of facts concerning water buffaloes and elephants.

Concerning the water buffalo C. O. Levine²⁶ writes as follows: "The mature animal has very little hair on its body. The sides back and thighs of the animal are almost bare of hair. The shoulders and knees have the most hair where it is about 2 to 3 inches long. The buffalo calves are born with a rather heavy coat of long, rather soft, dark hair all over the body which gradually disappears after one year of age is reached and is replaced by shorter and coarser hair thinly distributed over the body."

Concerning the elephant, G. H. Evans²⁷ writes as follows: "The hairs are bristly in character stiff to the touch and firmly rooted and are more abundant in certain localities. In the adult they are numerous on the forehead lower lip upper lip orifices and the ears and end of the tail. On the latter they are larger and stiffer in character and grow from the anterior and posterior borders and tip extending much higher up on the anterior where they are usually longer. Young elephants usually have much more hair about them than adults."

One may perhaps emphasize the point that in respect to paucity of hair the infant and baby elephant are as closely related as the milks of their mothers seem to be in protein-total calorie proportions.

as such. It is only suggested then, that while the ash of human milk is very low in relation to total energy value the figures expressing the relationship of ash to protein energy for the milk studied although not constant, are strikingly near the same order of magnitude.

In contrast to the constancy exhibited by the protein fraction of the total energy value of the milks studied (that of the human being excepted) the proportions in sugar and fat show the most extreme variations from the very high fat and low sugar of reindeer and water buffalo milk to the low fat and high sugar of the milk of the ass and of the horse.

Likewise there are wide variations in the water content of these milks as shown by the extreme fluctuations in the calorie value per 100 cc.

GENERAL COMMENT

The primary nutritional requirement of the organism is energy. It seems to the author that although the biological significance of the data submitted in this paper is obscure the facts may be linked with some of the so-called "laws" of energy metabolism.

Rubner formulated the law that metabolism is proportional to the superficial area of the animal. Even with variation associated with species, degree of maturity, growth size and sex, it is remarkable how narrow is the range through which this proportion moves. Man apparently, is not an exception to this law.

Rubner finds in all species the constant retention of approximately the same percentage of the energy ingested which averages 34.4 per cent, except in the case of man, in whom the energy retained for growth is only 5.2 per cent. (Lusk¹³ p. 571)

Furthermore, Rubner formulated a "law of constant energy expenditure" as follows: "The amount of energy (calories) which is necessary to double the weight of the newborn of all species (except man) is the same per kilogram no matter whether the animal grows quickly or slowly" (Lusk¹³ p. 567)

To these formulations none of which of course are mathematically rigid may be added from this study the statement that instead of the rate of growth of the suckling being correlated with the amount of protein and salts in the mother's milk the facts seem to be (1) that for many sucklings* infants excepted the proportion of the total energy intake in protein is the same for all species (20 per cent) when the sole source of food is the mother's milk and (2) that the inorganic salts in relation either to the milk or protein calories while not constant, shows no correlation whatever with the rate of growth of the young.

One may ask to what extent a prolonged period of immaturity in the infant enters as a factor in this matter. Certainly, under natural conditions, the young of all the animals studied receive other food than the

*I refer, of course, only to the sucklings of those species of animals studied in this paper in whom acceptable analyses of milk are available.

mother's milk at an earlier age than does the infant. The question raised cannot be answered here, but I should like to call attention to the interesting chart of Brody²⁸ (Chart 3, Lusk,¹⁵ p 570), which shows a remarkably constant pattern for the growth curve of a number of animals, but when the growth curve of man is plotted on the same basis the exceptional nature of the human curve is brought out. However, this eccentricity of the human curve is evident only for the long period prior to puberty. Thus exceedingly long period of development for the human young between birth and puberty seems to have laws peculiar to itself.

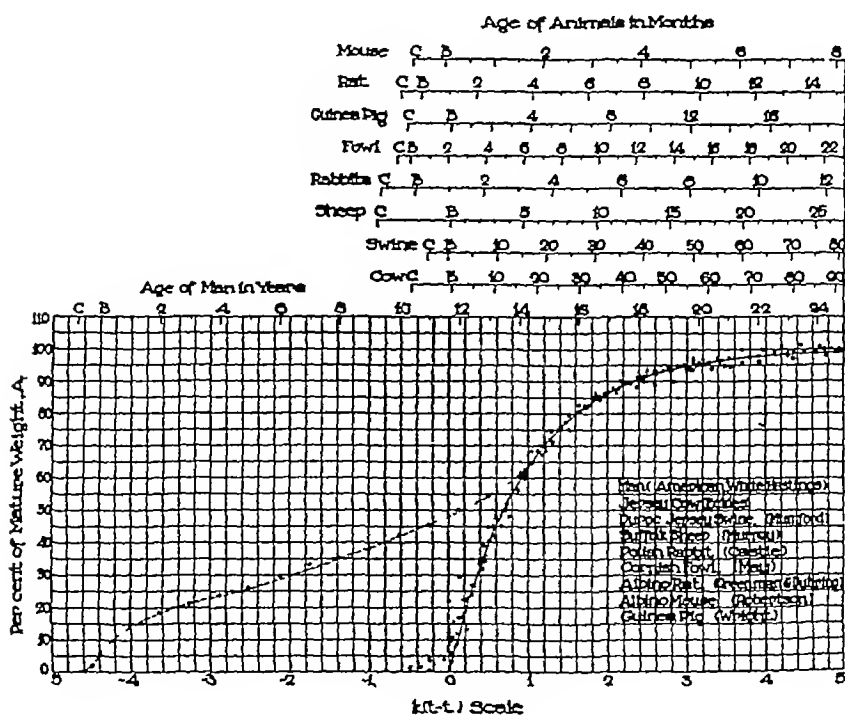


Chart 3—Age of animals in months—The growth curves of all domestic animals have the same shape and there are no graduations between man and animals. It is extremely desirable to determine the position of growth curves of primates other than man with respect to man on one hand and other animals on the other. The upper axes represent ages in absolute units (months for animals and years for man). *C* represents conception and *B*, birth. The numerals on the lower axis represent relative units (Brody).

Whatever may be the biological significance of the constancy which the protein fraction of the total energy value of the milks of many species of animals exhibits, the fact that human milk is a striking exception may be a phenomenon associated with what Professor Lusk called "the biological distinction of the protoplasm of the growing human being, which separates it from that of the lower mammals" (Lusk,¹⁵ p 572).

SUMMARY

The data of Abderhalden showing an alleged correlation between the rate of growth of sucklings and the protein and ash of the milk of the species have been analyzed from the standpoint of the percentage of the total calories in protein, carbohydrates and fat, also, attention is called to the relationship of the ash and some of its constituent salts to calories of milk and of protein

Additional data, similar to those of Abderhalden have been analyzed in the manner just indicated

According to the method of evaluation set up in this paper there is no correlation between the rate of growth of the suckling and other factors presented in the Abderhalden Table and in additional data

With the striking exception of human milk, the percentage of the total calories in protein is uniformly close to twenty for the milks of a number of species of animals

In human milk, by contrast, the percentage of the total calories in protein is less than ten

The biological or other significance of these facts is obscure Because of possible phylogenetic implications the milk of other animals—primates in particular—should be studied in the manner indicated in this paper

SOURCES OF DATA IN TABLES III, IV, V, VII AND VIII

Man

Composition of Milk Holt et al., 22.

Water Buffalo

Composition of Milk Levine C. O., 20

Composition of Ash of Milk Kunitz, 23, p. 66.

Rate of Growth Data supplied by Mr. To Shuo Tsai of the Department of Animal Husbandry Canton Christian College, Canton, China, through Dr. William W. Cadbury personal communication, October 15, 1925. The work was carried on under the direction of Mr. C. O. Levine

CALF NO.	BIRTH WEIGHT	SUBSEQUENT WEIGHTS	DAYS REQUIRED TO DOUBLE BIRTH WEIGHT*
3	63 lb	181 lb on 130 day	120
4	85 lb	170 lb on 145 day	145
6	76 lb	153 lb on 112 day	112
8	60 lb.	122 lb on 131 day	131
10	71 lb	140 lb on 75 day	75
11	60 lb	140 lb on 77 day	60
Indian Buffalo Calf	85 lb	190 lb on 120 day	100
Average			100

* Estimated by means of straight-line graphs.

Dr. Cadbury's communication states: "All calves were removed from their mothers at birth and milk was milked from the mother and fed to them for the first month at the rate of one pound of whole milk to 10 lb of body weight of the calf for the first month. After this first month one-half pound of whole

milk and one half pound of soy bean curd, mixed, were fed to the calves for ten days. Then one third whole milk and two thirds soy bean with some bran added were fed for ten days. Finally a total of one pound of milk daily and bran beer constituted the calves' food."

Cow

Composition of Herd Milk König, 24, p 219

Composition of Ash of Milk Holt, et al., 22

Composition of Milk of Special Dairy Breeds Rogers, 25

Rate of Growth Eckles, C H, Chief, Division of Dairy Husbandry, University of Minnesota, 26, and personal communication June 23, 1925

Ass

Composition of Milk König, 24, p 394

Composition of Ash of Milk König, 24, p 394

Rate of Growth Through the kindness of Professor Marfan I received the following data from M. Barrier of Alfort, France

Average weight of ass at birth

Small African race—15 K

Small race from south of France—30 K

Large race (Portou)—25 K.

This weight is doubled in from 45 to 60 days

In a personal communication, Dr. Sidney Kahski of San Antonio, Texas, states that a "leading veterinarian" informed him that the burro doubles its birth weight in 6 weeks

Horse

Composition of Milk König, 24, p 393

Composition of Ash of Milk König, 23, p 663

Rate of Growth Mr. H. H. Reese, Animal Husbandry Division, U. S. Dept. of Agriculture informs me from actual observation on a Morgan colt that the birth weight was doubled in 42 days

Reindeer

Composition of Milk Ylppo, A., 27

Composition of Ash of Milk König, 24, p 395

Rate of Growth

OBSERVATION	BIRTH WEIGHT	BIRTH WEIGHT DOUBLED IN
1	35 to 4 Kg	35 days
2	40 to 5 Kg	38 days
3	40 to 5 Kg	28 to 35 days
	Average	31 days

This information was secured by Professor E. A. Park, Nov. 30, 1925, through the kindness of Mrs. Carl Bassoe of Norway, from Messrs. Kristian Nissen and Arne Arnesen of the Inspektoren for Rendriften, Oslo, Norway

Goat

Composition of Milk König, 23, p 351

Composition of Ash of Milk Abderhalden, 6, p 457, 458

Rate of Growth In personal communication, October 7, 1924, Professor Pierre A. Fish, or Department of Veterinary Physiology, New York State Veterinary College, Ithaca, N. Y., informed me as follows concerning two kids (sisters) "of a breed partly Saanen"

BIRTH WEIGHT	BIRTH WEIGHT DOUBLED IN
20 Kg	20 days
17 Kg	23 days
Average	22 days

Sheep

Composition of Milk König 24, p 371

Composition of Ash of Milk König, 23 p 660

Rate of Growth In a personal communication July 7 1924 Mr D A Spencer of the Animal Husbandry Division of the U S Department of Agriculture informs me that sheep double their birth weight in about 14 days.

For

All data from Young and Grant, 29 p 805

Camel

Composition of Milk In a personal communication, June 14, 1920 Lt Col McCarrison of the Pasteur Institute Coonoor, S India, gave me two analyses of the milk of the camel These analyses were made by Dr P E Lander, Agricultural Chemist to the Government of the Punjab I have taken the average since the analyses were nearly the same

Composition of the Ash of Milk König 23 p 662

Llama

Composition of Milk König 23 p 661

Culnea Pig

Composition of Milk and Rate of Growth Abderhalden, 6 p 437 458

Elephant

Composition of Milk

(a) König 23 p 664

(b) Heineman 28 p 76

(c) Doremus 29, p 486

Zebr

Composition of Milk König 23 p 661

Blue Whale (Balaeonoptera Sibbaldi)

Composition of Milk König 24 p 400

Bartenwhale (Family Balaeoniden)

Composition of Milk König 24 p 400

Monkey (Mangabey)

The author is fortunate in being courteously permitted to use some preliminary observations of Dr Gertrude van Wigenen (Department of Obstetrics and Gynecology) and Dr Harold E. Himwich (Department of Physiology) of Yale University Ten samples of milk were obtained each sample amounted to a cubic centimeter and was a complete milking Some samples were used for the protein determination and others for carbohydrate fat and ash respectively The data in the table are averages of at least two analyses.

BIBLIOGRAPHY

- 1 Powers Grover F Am J Dis Child 33 181 1926
- 2 Bruge C Text Book of Physiological and Pathological Chemistry Translated from the 4th German Edition by F A and E H Starling Philadelphia, 1902 P Blakiston & Son & Co.
- 3 Pröschner Fr Ztschr f Physiol Chem. 24 28 1898
- 4 Idem Ibid. 26 487 1898 99
- 5 Idem Ibid. 26 493 1898 99
- 6 Idem Ibid 27 408 1899
- 7 Idem Ibid. 27 504 1899
- 8 Abderhalden, Emil Text Book of Physiological Chemistry Translated by William T Hall and George Defren 1st Edition New York 1908 John Wiley & Sons
- 9 Minot Charles S. The Problem of Age Growth and Death New York, 1908 G P Putnam's Sons p 168

- 10 Czerny, A. D, and Keller, A Des Kindes Ernährung, Ernährungsstörungen und Ernährungstherapie, ed 2, vol. 1, Leipzig and Wien, 1923, Franz Deuticke, p 73
- 11 Finkelstein, H Lehrbuch der Säuglingskrankheiten, ed 2, Berlin, 1921, Julius Springer, p 114
- 12 von Pfannöcker, M, and Schlossmann, A Handbuch der Kinderheilkunde, ed 3, vol 1, Leipzig, 1923, F C W Vogel, p 365
- 13 Henbner, O Lehrbuch der Kinderheilkunde, ed 3, vol. 1, Leipzig, 1911, Johann Ambrosius Barth, p 73
- 14 Meyer, L F, and Nassau, E Die Säuglingsernährung, München, 1930, J F Bergmann, p 35
- 15 Lusk, Graham The Elements of the Science of Nutrition, 1928, ed 4, W B Saunders Co
- 16 Sherman, Henry C Chemistry of Food and Nutrition, ed 4, New York, 1932, The Macmillan Company, p 249
- 17 Starling, E H Principles of Human Physiology, ed 5, edited and revised by Evans & Hartridge, Philadelphia, 1930, Lea & Febiger, p 1012
- 18 Hammarsten, O A Text Book of Physiological Chemistry, translated by Mandel from the 8th German edition, New York, 1922, John Wiley & Sons, p 667
- 19 Powers, Grover F Am J Dis Child 30 453, 1925
- 20 Levine, C O The Water Buffalo for Dairy Purposes, Lingnaa Agricultural Review, vol. 1, No 1, December, 1922, Canton Christian College, Canton, China
- 21 Evans, G H Elephants and Their Diseases, Superintendent, Government Printing, Rangoon, Burma, 1910, p 73
- 22 Holt, L Emmett, Courtney, Angeha M, and Fales, Helen L Am J Dis Child 10 229, 1915
- 23 König, J Chemie der menschlichen Nahrungs und Genussmittel Band II. Die Menschlichen Nahrungs und Genussmittel, ed 4, Julius Springer, Berlin, 1904
- 24 König, J Chemie der menschlichen Nahrungs und Genussmittel Nachtrag zu Band I A Zusammensetzung der tierischen Nahrungs und Genussmittel, Julius Springer, Berlin, 1919
- 25 Rogers, Lore A Associates of—Fundamentals of Dairy Science, The Chemical Catalogue Co, Inc, New York, 1928
- 26 Eckles, C H Normal Growth of Dairy Cattle, Research Bulletin 36 Agricultural Experiment Station, College of Agriculture, University of Missouri, April, 1920
- 27 Marfan A B Traité de L'Allaitement et de L'Alimentation des Enfants du Premier Age, ed 3, Paris, 1920, Masson et Cie, p 28
- 28 Robbins, Brody Hogan, Jackson, and Greene Growth, New Haven, 1928 Yale University Press
- 29 Young, E G and Grant, G A J Biol Chem 93 805, 1931

THE TREATMENT OF POLIOMYELITIS PAST AND PRESENT

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THE question of the treatment of poliomyelitis resolves itself into two parts, one the specific treatment by serum or other means as yet unknown, the other the management of the end results of the lesions in the nervous system

The specific treatment may be said to date from 1910 when Netter, Gendron and Touraino used convalescent serum. Various other serums have been suggested and used, such as normal horse serum, pneumococcus serum and the like and serums prepared in horses or other animals using streptococci, as the serum of Rosenow reported on first in 1917. Animals have also been immunized to material taken from monkeys paralyzed by poliomyelitis by Neustädter and Banahaf, Pettit, Weyor, Park and Banahaf, Fairbrother, and Fairbrother and Morgan. More recently serum from adults has been used. The results vary. Those who have used the serums most are inclined to believe that the serum from patients who have been left with residual paralysis has a definite, if weak, power of preventing or limiting the paralysis if given in the preparalytic stage. Others, also basing their judgment on experience, are sceptical as to its value. As yet no satisfactory large series of cases treated with a like series of control cases has been reported. There have been some series of cases treated and controls reported but these for one reason or another are open to criticism. The question of the value must be regarded as an open one. It seems to be on a theoretically sound basis, and from such studies as Macnamara's it would seem possible to prepare a serum which if administered sufficiently early in large enough quantities would give as good results as she has obtained.

About the management of patients who have had the disease there has been and still is a considerable difference of opinion. John Hunter suggested the value of the exercise of the will in training muscles that had been paralyzed but not in regard to poliomyelitis although he records at least one case which he had observed. Underwood and the physicians who shortly followed him made no therapeutic suggestions of value beyond the use of 'irons to the legs' and Samuel Merriman, who edited one of the later editions of Underwood's book, said, "It may be doubted whether irons to the legs can ever be useful in a state of paralysis of the lower extremities. If the limbs are paralytic, how are irons to the legs to enable the patients to walk?" This was two years after John Shaw had written his interesting book "*On the nature and treatment of the distortions to which the spine and the bones of the chest are subject*" Shaw

used methods of stretching and exercises not unlike some methods employed today and some of his cases were undoubtedly of poliomyelitic origin. W. J. Little used tenotomy and manipulations, and many of his cases were due to poliomyelitis. Had he had the sharp eye and understanding brain of Jacob Heine he would have made a name for himself in infantile paralysis as well as in Little's disease. Jacob Heine, in 1840, in his *Beobachtungen über Lahmungszustände der unteren Extremitäten und deren Behandlung* laid the firm foundations of the correction of paralytic deformities by the use of apparatus, exercise and strengthening the entire body. He used warm baths and steam baths before manipulation, and when he could not get rid of the contractions he used tenotomy which had been suggested by Delpech in 1823 and perfected by Strohmeier a little later. Heine also used exercises for the muscles and devised machines to help the patient and figures one of these machines in his plates. His orthopedic apparatus is the same in principle as that used today and very much the same in execution. In 1860, in a second edition of his book, he called attention to the possibility of preventing deformity by suitable apparatus. Eulenbeig in 1859 made a table of the deformities and the muscles which were paralyzed and those which were antagonistic, with a view to exercise, and Ling in Sweden developed his system of so-called Swedish exercises or Heilgymnastik. The latter spread rapidly over the world. The Hungarian, Matthias Roth, one of Ling's students, introduced the system into England, and Charles Fayette Taylor brought it to America. But almost everywhere physicians and surgeons, much as they often do now, used only one part of the therapeutic armamentarium, Ling his exercises, Roth various methods including apparatus for support, many of the orthopedic surgeons depended on apparatus or operations or both together and neglected exercise. Duchenne of Boulogne about 1850 began to develop the use of electricity, about which he was more enthusiastic than any one of his time or after. He also used apparatus of great ingenuity for replacing or supporting paralyzed muscles. Moritz Meyer was another great exponent of the use of electricity.

The greatest genius among those dealing with infantile paralysis in those days, and, indeed, no one has surpassed him, was Charles Fayette Taylor, founder of the New York Orthopedic Dispensary and Hospital. He early became interested in the protection of bones and then of muscles. In 1867 he published a little book of 119 small pages which is without doubt one of the great American medical classics, a book of such rarity that few libraries have a copy. It is a book evidently not appreciated fully in its own day and now practically unknown but one which contains all the principles of the proper management of a case of poliomyelitis as far as the care of the apparatus of locomotion and station is concerned. The principles of treatment as laid down by him have been in part used by others, but for the most part they are just

being rediscovered today. Some little of his work has found its way into medical and surgical textbooks for the most part writers from his time on have failed to stress the essential points. Sechgmüller, in Gerhardt *Handbuch der Kinderkrankheiten* in 1850, outlined the therapy in a masterly way omitting however some points of great importance. In the recuperative stage he advised among other things electricity, massage given to the paralyzed muscles, heat spray and steam douches, warm baths, hydrotherapy, and in the chronic stage electricity, massage exercise hydrotherapy and the like together with apparatus and such helps as crutches walkers and exercising machines. He mentions the use of apparatus to prevent deformities and contractures but does not stress this point sufficiently.

Wharton Sinkler in the otherwise excellent article in Keating's *Cyclopedia of Disease of Children* in 1890 advised electricity and massage and the use of the affected parts and urged that the child be made to walk as soon as possible. He makes no especial mention of the use of apparatus to prevent deformity but suggests its use after it has occurred.

From that time on but few spoke and when they did it was like the voice of one crying in the wilderness. We may mention Hugh Owen Thomas and Sir Robert Jones who insisted on the correct methods and Colin Mackenzie, too taught muscle reeducation and muscle protection but otherwise the therapy of poliomyelitis seemed at a standstill except that the orthopedic surgeons were able to do more and better operations for the correction of deformities but their prevention was not stressed by many and as a rule the patients were not given sufficient rest and were allowed to walk too soon. In 1917 Lovett¹ published his observations on 1836 cases and showed that weight bearing in the first year, where trunk and legs are involved is risky and advised *ambulatory exercise only when complete recovery has occurred or when there is reason to believe that hope of complete recovery or further substantial gain must be abandoned*. It might be added that this is to be based on frequent examinations of the muscles and not any time factor. In a recent article on "Physical Therapy in Infantile Paralysis," the author states, "In any case after six or seven months it is generally advisable to allow getting up on the feet for the effect of the general condition and morale even though the length of time daily may be restricted. Cases which have not responded to treatment should be started walking for the same reason. This statement is calculated to do very considerable harm to many patients—as noted below. The writer be it said to his sinful sorrow has been guilty of misleading statements on this point which he has since learned from experience are wrong. The lack of exact statement in most textbooks and indeed in many articles is rather remarkable in view of the amount of recent study of the subject

Let us look for a moment at the work of Taylor and note how completely he covered the ground as far as principles of treatment are concerned. His views as to the pathologic conditions may be disregarded, since little was known in his day. He noted, as did Heine, that all cases tend toward recovery. "Very few cases are to be met with where some portions of the originally paralyzed members have not entirely recovered." He questioned why more patients did not show greater recovery when the tendency was that way and came to the conclusion "that it is not always because Nature has wholly exhausted herself, but because accidental circumstances have come to interfere with her work, which would otherwise have gone on much further." He noted the contractures of the muscles and the deformities and said "I reply, without hesitation, that contractions and distortions are *not* necessary consequences of this paralysis, that these unhappy results are always and entirely preventable. Indeed, what seem to be contractions of certain muscles—generally flexors—are not contractions at all, but simply a mechanical shortening of the muscles when their attachments are for a length of time brought closely together. But in infantile paralysis, the shortening of certain muscles is not the first or principal damage done by improper and careless positions of the paralyzed limbs. The shortening, though the most noticeable, is not the first or worst complication which arises to arrest the progress of improvement and to set in train a series of conditions favoring the formation of distortions and deformities. Any position of a limb which allows the extensor muscles to become shortened must inflict a worse damage on the flexors by keeping them extended till they lose their remaining irritability and become degenerated. Now, we have another fact connected with these cases when they have arrived at the stage of deformity, viz, this: the difficulty of treatment consists much less in relaxing the shortened muscles than in giving tone and strength to their antagonists—the lengthened and weakened ones. Indeed, it is this, in the destruction of all remaining irritability, and in many instances the destruction and entire loss of the substance itself of the expanded muscle, which constitutes the principal anxiety in treating this class of deformities. As this important consideration has been many times neglected, if not entirely lost sight of, let us consider the effect of simple extension upon the power and function of muscular tissue in its healthy state."

He goes on to point out that "To retain a healthy muscle in an expanded state for a certain length of time is to diminish or destroy its irritability and contractile force. To extend a muscle while in the act of contracting, that is, to overcome it, is to, *at once*, destroy its irritability and force." He uses as illustration the stretching of the sphincter ani as is frequently done for the relief of fissures, etc.

The mechanics of the production of deformities through the imbalance of muscles and weight bearing too early is clearly set forth and by

proper care the deformities are always preventable. "If the feeble muscles and ligaments of the joints were not subjected to overwhelming strain, by bearing too early an injudicious weight, they would not give way under the first attempt at exercise, instead of being strengthened by it—which they might be, if proper precaution were observed. The treatment of infantile paralysis in the early stages consists for the most part, in *noninterference* with the recuperative efforts of Nature. We are to remember how little it may take to injure the enfeebled muscular tissue and diligently guard the patient from possible harm—knowing the direction from which injury is most likely to come."

The recuperative period is a very critical period, and it is difficult to know when to exercise the muscle and how much. If it is not used it will waste from nonuse, and if too much is given it will be destroyed by overuse. "Evidently, then, we must contrive to afford the muscles to act *within their capacity*—alike avoiding inactivity or overaction—until their development has reached the point where they are capable of being made available in sustaining the weight of the body in locomotion. *We must furnish the muscle an exercise that shall not exceed its capacity.* And not until the powers of the muscles have been developed till they are equal to sustaining the weight of the body should they be required to sustain it. There is no physiological principle more clear or simple. The leg of a paralyzed child in relation to its body may be compared to those of an infant called upon to support the trunk of a man, they cannot do it, and should not be allowed to attempt it till they have grown equal to their load. But every particle of latent force calls for use, action is its life and growth and under these unusual circumstances we are called upon to furnish the opportunity for whatever force there is to act.

"If the patient has been carefully attended, so that no damage is done by faulty positions while in a state of muscular atony there will be no difference in the rate of recovery, nor will there be shortening or lengthening of different muscles and the patient can begin to stand and walk at a much earlier stage, and with much less strength than when a very small amount of shortening has been allowed to take place. The reason for this is that the least contraction of the flexor muscles will at once throw the patient out of his natural position and the weight of the body must be *held entirely* by the force of the muscles instead of resting on the bony framework, with only sufficient muscular aid to keep it erect."

It will be seen that the principles of the treatment of poliomyelitis were laid down with great accuracy and clarity but with but few exceptions until recently these principles have been disregarded. C. L. Lowman and Jean Macnamara in addition to those noted above may be mentioned among those who have striven to spread this gospel of the prevention of deformity and the protection of muscles which may be

accomplished by the early use of proper splints to hold the body and the limbs in line and at the same time to give relaxation to the paralyzed muscles. In all paralyzed patients the most important muscles should be favored first until their recovery is assured. These are the deltoid, extensors of the wrist, the opposers of the thumb, the glutei, the quadriceps, the calf muscles, tibialis anticus and the abdominals. These must be placed at rest in a relaxed position, which is in recumbency in the same position the body would be if standing erect. Stretching of the muscle should not be allowed in handling the child as is so frequently done. It must be remembered that in the early stage and as long as improvement is looked for, rest is the most important thing. Fatigue both general and local must be guarded against. When the time comes to start exercise, it should be begun with very little and always kept well within the capacity of the muscle. Passive movements may be made when the movements are too much for the patient and the patient wills the movement at the same time. This is important for volitional movements are the ones which build up the muscle power. Assistance must be given and support, as well, in making movements with weakened muscles. As the power returns great care should be taken to exercise only the muscles which need it and to make such changes in the splinting from time to time as may be needed by the change in balance of power due to improvement. Great care must be taken to keep the body in line to permit of good posture when the time comes to stand.

The nature of the splints will vary with the muscles involved. The modified double Thomas splint as suggested by Maenamara² will be found useful, since this permits the patient to be kept in line with such adjustments as may be needed in the arms and legs. The abdominal muscles are looked after by a corset and the support extends from head to foot. Legs and arms that are affected should never be left to dangle even for a moment. Eternal vigilance is the price of the best recovery.

Muscle training is best carried out by a trained physiotherapist well grounded in anatomy and muscle function, but as this is impossible in most cases which must be treated at home, the simpler movements may be taught some member of the family and the treatment carried on under as close supervision as possible. Too little exercise is better than too much, and patient, family and assistants must be warned as frequently as possible on the dangers of doing too much. Exercise in warm water is much used in various places provided with suitable pools, and it can also be given in a large bathtub or a Hubbard tub. In the water gravity is largely eliminated and volitional movements can be made that would otherwise be impossible without assistance. This helps the morale of the patient. The principles of muscle protection must always be borne in mind, water or no water. In giving exercises the arc of motion should always be completed even if assistance is needed. Care

should be taken to see that the patient uses the muscles to be exercised and not some other one, as may be done if the patient is not carefully supervised. The amount and the kind of exercise must be modified to suit changes in the condition. With trunk and legs affected weight bearing should not be permitted as long as improvement is going on if the best results are to be obtained. Patients seen late should begin like patients in the acute stage. Muscles that have been damaged by too much use should be allowed to rest in positions allowing the attachments to come as close together as possible and thus make for relaxation. Eventually there will come a time when it is evident that there is to be no further improvement, and then with suitable braces the patient may be allowed up and the treatment directed toward getting as good functional use of the body as is possible. Much can often be done in late cases which have been neglected, for often the muscles have been allowed to atrophy from disuse although at present there are more spoiled by too much exercise rather than by too little.

It is important to keep the paralyzed limbs warm so as to favor growth, and additional heat should be applied before exercising and once or twice daily in the form of dry heat applied by placing the child or the parts in a tent or box provided with carbon bulbs. Fresh air and sun baths or ultraviolet ray in the absence of sun is a useful adjuvant in maintaining general nutrition.

Gentle massage is useful in maintaining the nutrition of the muscle, but it should not be used until all tenderness has disappeared and then with caution and the severe hard massage of the professional operator avoided.

Warm salt baths may be given daily and are useful in the tender stage to allay the pain and soreness. Children may be bathed in a tub if great care is taken that affected muscles are not stretched. Macnamara advises bathing adults in bed by placing a rubber sheet under them and pinning it with clothes pins to boards hinged to the side of the bed, to the foot and by passing it over pillows to the back of the bed. The water is drained by pulling a part of the sheet through a hole in the board and when not in use the boards are dropped to the side of the bed. Any mechanic can attach gadgets to the bed to allow the use of wires for the same purpose.

It is important to keep up the morale of the patient, a thing often neglected. Pity should not be expressed to the patient for it develops the habit of self pity which is most destructive to the patient's mental well being. Suitable amusements, and when ready for it education by teachers or by mail games and visitors should be allowed the patient. Moderation should be practiced in all things. Only too often patients are left entirely to their own devices and fret and worry in consequence.

when a little forethought would render the patient happy and contented, for poliomyelitis victims tend to be cheerful if conditions are at all favorable

The chief points may be summarized as follows

1 The tendency is to recovery, much of the permanent paralysis is due to neglect or improper management

2 Contractions and deformity can be avoided.

3 The principal thing in the treatment is rest with the body recumbent but in the position it would be in if standing erect

4 The most important muscles should be favored early and until their recovery is assured

5 Special adjustments of splinting must be made to favor muscles which should have it

6 Fatigue general and local should be avoided

7 Weight bearing should not be allowed as long as recovery is expected.

8 Especial care should be taken not to allow at any time any stretching of affected muscles

9 When recuperation is well established, carefully supervised exercise within the capacity of the muscle is of value

10 Warm salt baths, very gentle massage (only after all tenderness has disappeared), fresh air and sunlight and warmth are valuable adjuvants in treatment

11 The splints or braces should be inspected frequently and changed to suit conditions

12 The transition to weight bearing should be gradual, avoiding overexertion and fatigue

13 After all the improvement has been obtained that can be looked for as judged by a failure to improve under proper management, the patient should be gotten on his feet, using such apparatus as may be necessary. Old and neglected cases will need orthopedic care to correct deformity and exercise to develop latent muscle power

14 Every case should be treated individually and not by any fixed routine. Changes should be made to suit conditions as they arise and deformities due to lack of balance of muscles carefully avoided

REFERENCES

- 1 Lovett J. A. M. A., June 21, 1917
- 2 Macnamara Brit M J 2 1099, 1932

11 EAST CHASE STREET

THE INFLUENCE OF FRUIT AND VEGETABLE FEEDING UPON THE IRON METABOLISM OF THE INFANT

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THE iron metabolism of the growing young has been a question of interest ever since the epochal publications of von Bunge¹ over fifty years ago. His findings that both breast milk and cow's milk are exceedingly low in iron content and inadequate to cover the iron requirement of the growing organism have not been challenged to this day. It was he who first laid the foundation for the conception of reserve depots of minerals among them notably iron in the growing organism of the young animal to be available when needed during the exclusive milk period.

Inquouenq² and, at a somewhat later period, Czerny³ developed this same conception for the newborn and young of the human species and the latter first called attention to a characteristic alimentary anemia which develops when the young growing organism is deprived of adequate iron intake in its food.

The findings of Hart, Steenbock, Elvehjem and their coworkers⁴ and the work of Whipple, Robscheit Robbins and others⁵ stimulated a great deal of interest in the subject of alimentary anemia and has in recent years led to a series of splendid investigations in this field.

The conception that foodstuffs notably high in iron content, should be curative for alimentary anemia or should be particularly suitable for the replenishment of deficient iron reserves in the organism of the young dates back to the investigations of von Bunge¹ and is the basis of a feeding régime for the young infant first suggested and championed by Czerny³ and now quite generally used in many parts of the civilized world.

The demonstrable high organic iron content of some vegetables and certain fruits suggested them strongly as suitable early dietary additions to prevent the onset of or combat an already existing alimentary anemia. To these were added later for older children, glandular organs, such as liver or kidney the favorable action of which was recognized by Czerny and others³ long before the publications of Minot and his coworkers,⁶ although the exact mechanism of such favorable action was not understood at that time.

The investigations of Hart and Steenbock⁴ finally showed the remarkable effectiveness of combinations of iron salts and traces of copper in the treatment of alimentary anemias and indicated that

these substances alone, or preferably in combination with some of the foodstuff mentioned, were a very superior form of treatment for alimentary anemia

The relative degree of effectiveness of these various procedures in combating alimentary anemia was a part of this study, but its principal aim was the study of actual iron retention in the young growing organism to whose dietary were added high iron containing food in the form of vegetable fiber and fruit

In an earlier paper⁴ we had studied the effect of vegetable feeding upon the mineral metabolism of the young infant. This included a study of the effect on the iron balance of two of the infants. Those results gave no evidence of a beneficial effect upon the iron retention of feeding dried or pureed spinach. It was felt however, that the evidence was too meager and that the study should be continued with other infants. We are now ready to report results of additional metabolism experiments on three normal infants, ranging in age from five weeks to seven months, and also on one infant diagnosed as a nutritional anemia case. As in the earlier work, the vegetable studied has been spinach in the dried, pureed, and raw forms. The experiments have been extended to include the effect of apricots which Whipple and Robschert-Robbins⁵ found more effective than spinach and other vegetables and most other fruits in curing the anemia of their dogs. In the case of the anemic infant, it has also included the effect of adding wheat germ extract, a mixture of ferric and cupric salts and liver

We have attempted to make the experiments as nearly accurate as possible. With very few exceptions, the periods on metabolism have lasted six days. In the case of the anemic infant, the period on milk formula only, used as a control, lasted four days because it was felt that the giving of iron-containing foods should be started as soon as possible

As a rule the normal infants were very regular in their elimination of feces. No metabolism period was begun until the infant had been receiving a given diet for at least five days so as to insure that its system had reached equilibrium in regard to that diet. Two or three consecutive metabolism periods on a given diet, with one or two days intervening, were run in each case in order to find out what variations may be expected normally when the diet remains constant

The iron content of the various foods was determined by analyses. Twenty-five pound cans of powdered milk furnished a uniform stock supply of milk for each infant. The sugar used in the formula was found to contain traces of iron. The amount of milk powder and sugar was increased as the infant grew, but was kept constant throughout a given control period and the following periods in which the supplement of spinach or apricots was added. The dried spinach was

also provided in large lots, each of which was analyzed. The anemic infant was given eight grams daily, the normal infant six grams. The pureed spinach was provided in lacquered tin cans holding a little more than enough for two days' feeding. While a large supply from the same factory batch was on hand and every effort had been made to keep the contents uniform, we felt we obtained a more accurate knowledge of the iron intake by combining together twenty gram samples from each can used and analyzing the composite sample for iron. The same held true for the raw spinach. The infant's daily allowance of raw or pureed spinach was seventy grams. Dried apricots were used. They were softened by heating with distilled water on the steam bath and ground to a fine pulp in a porcelain mortar. A composite, representative of each period, was analyzed for iron. With one exception, the equivalent of forty grams dried apricots were given to the infant daily. Infant No. 3 received the equivalent of 67 gm of dried apricots daily in the seventh period. The wheat germ extract was supplied from a large stock solution which had been analyzed for iron content. A water extract equivalent to 16.2 gm wheat germ was given daily. Iron and copper salts were given to infant No. 4 in the last two periods in daily doses of 6 cc of a 10 per cent solution of ferric ammonium citrate (100.8 mg Fe) and 1.5 cc of a 0.2 per cent solution of copper sulphate (0.76 mg Cu). Liver was freed from connective tissue, ground to a pulp and cooked by boiling for a few minutes. The daily allowance of liver was 20 gm. Iron was determined in a composite sample for each metabolism period.

As in our earlier experiments the milk formula contained definite weights of powdered milk and sugar made up to a definite volume with distilled water. Any supplement such as the spinach or apricots was mixed with the milk formula to insure its being entirely consumed. In a few cases especially with the apricots, difficulty was encountered in getting the infant to take all the formula. Either he refused to take it or if forced, regurgitated a considerable amount. All refusals for a given period were collected. If small in amount they were transferred to a platinum dish, dried, ashed and the ash dissolved in a known volume from which an aliquot was taken for analysis. If the amount was too large for such treatment it was evaporated to dryness in a porcelain evaporating dish on the steam bath then in an oven at 105° C. the residue weighed, ground up and mixed and a sample analyzed for iron. Regurgitations were caught on masses of weighed gauze and the amount of iron lost in this way calculated from the increase in weight of the gauze and the known composition of the milk mixture assuming one gram gain represented one cc of the mixture lost. This, of course, introduced an error but a liberal allowance of 10 per cent error in calculation of iron in the regurgita-

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these precautions, the obtaining of good checks on duplicate ash solutions meant that any contamination by iron had been avoided.

Great difficulty was encountered in finding a suitable method for the iron determination. Almost without exception the methods usually advocated or used by various investigators gave uncertain results and exceedingly poor checks of the controls. This experience made us doubtful of some of the reported results, especially of the earlier work on iron.

The method finally used for determining iron was a modification of Stugart's method. It involved carefully controlled dry ashing in a muffle furnace whose temperature was automatically regulated at 400°C , solution of the ash, partially with N hydrochloric acid and partially, after reashing the residue over the free flame by fusion with sodium carbonate, acid hydrolysis of the ash solution to convert pyrophosphates to orthophosphate, and determination of the amount of iron by colorimetric comparison in amyl alcohol solution against a standard containing 0.02 mg Fe after adjusting the acidity of both solutions to the same strength and converting the iron to ferric thiocyanate. Platinum dishes were used for the dry ashing. The samples were slowly charred by starting them in front of the open door of the muffle furnace and pushing them back gradually, avoiding the rapid evolution of gas. With milk samples, a slow charring was made possible by mixing the powder with a small amount of water and caramelizing by heating overnight in an oven at 105°C before introducing into the muffle furnace.

RESULTS

The results of the experiments on normal infants are given in Table I and are shown graphically in Fig. 1 where the heights of the columns represent the values for total iron intake, the total iron output, and the difference between the two, the iron balance. We feel that the results bear out the conclusion we had reached in our earlier experiments, that the feeding of spinach to the young normal infant in any of the three forms tried does not appreciably affect the iron metabolism. We feel also, that the same may be said of the feeding of apricots. The iron balances for a diet of milk only vary within small limits for infant No. 1 all slightly negative for infant No. 2 all slightly positive and for infant No. 3 positive at first but in later experiments slightly negative.

The effects of puréed spinach were tested on two of the infants. There appears to be a slight increase in retention attendant upon the addition of the puréed spinach to the diet. If the four periods are averaged a balance of $+0.16\text{ mg Fe}$ as compared with $+0.04\text{ mg}$ the average of the four preceding periods on a milk diet and a larger

TABLE I
IRON METABOLISM OF THE NORMAL INFANT AS INFLUENCED BY THE FEEDING OF SPINACH AND APRICOTS

INFANT NO	PERIOD NO	NO DAYS IN PERIOD	NATURE OF SUPPLEMENT TO MILK DIET	HB gm per 100 cc	R B C millions	WGT OF DRIED FECES gm	TOTAL FE INTAKE mg	IF IN FECES mg	FE IN URINE mg	FF BALANCE mg
1	1	6	0			4.80	110	1.09	0.061	+0.01
	2	6	0	14.8	5.00	6.13	1.28	1.40	0.033	-0.15
	3	6	Spinach (puréed)			7.26	2.36	2.33	0.071	-0.04
	4	6	Spinach (puréed)	13.5	5.52	7.83	2.36	2.26	0.034	+0.07
	5	6	0			5.92	1.46	1.46	0.033	-0.03
	6	6	0	14.2	5.90	6.00	1.47	1.56	0.045	-0.14
	7	5	Spinach (raw)			12.96	3.97	3.97	0.021	-0.12
	8	6	Spinach (raw)	15.4	6.34	17.00	3.78	3.56	0.020	+0.19
2	1	6	0			4.80	1.14	1.03	0.026	+0.08
	2	6	0			4.58	1.29	1.03	0.041	+0.20
	3	6	0	11.0	4.18	4.64	1.29	1.22	0.024	+0.05
	4	5	Spinach (raw)			9.70	3.54	3.50	0.036	0.00
	5	6	Spinach (raw)	10.4	4.67	8.96	3.40	3.07	0.034	+0.30
3	1	6	0			6.09	1.37	1.21	0.037	+0.12
	2	5	0	15.5	5.72	6.84	1.39	1.19	0.034	+0.17
	3	6	Spinach (puréed)			9.93	2.23	1.89	0.038	+0.30
	4	6	Spinach (puréed)	12.2	5.18	9.94	2.23	1.88	0.040	+0.31
	5	6	0			8.52	1.63	1.49	0.038	+0.10
	6	6	0	15.3	6.10	9.26	1.63	1.57	0.038	+0.02
	7	6	Apricots			11.36	3.08	3.07	0.025	-0.02
	8	6	Apricots	9.4	6.02	13.55	3.42	3.44	0.038	-0.06
	9	6	Apricots			11.17	3.34	3.02	0.036	+0.28
	10	6	0	9.1	5.54	7.85	1.96	2.00	0.024	-0.06
	11	6	0	7.8	5.00	7.19	1.81	2.05	0.036	-0.28
	12	6	Spinach (dried)			11.01	3.42	4.06	0.038	-0.08

balance in three of the four spinach periods than in any of the preceding periods. However, these retentions are small and, we believe, insignificant.

The raw spinach, also tested on two infants, gave positive retentions in two of the four periods studied, while the balances in the preceding milk periods were either negative or if positive, less in amount. Expressed in terms of averages, a balance of +0.03 mg Fe on a milk diet was increased to +0.093 mg by adding raw spinach to the diet, but again, such a small retention would seem insignificant.

In the case of infant No. 1, a severe diarrhea developed as a result of the raw spinach. This was true to a lesser degree for infant No. 2. It is interesting to note that in the last period of infant No. 1 on raw spinach, there was a fair degree of retention in spite of the greatly increased output of feces. One would feel more optimistic about its favorable effect on iron retention if the first periods on raw spinach for each infant had given positive results. Taking all the effects into account, we feel that the feeding of raw spinach to the young infant is not to be recommended.

Only one metabolism period on dried spinach was tried on a normal infant. The results support our earlier findings that dried spinach, in spite of its high iron content, tends to decrease rather than to increase the iron balance. In this case, a negative balance of 0.68 mg resulted after adding the spinach to a milk formula on which the infant showed an average negative balance for two periods of 0.17 mg. Results of feeding dried spinach to the anemic infant also bear out the same conclusion. Of the three forms of spinach studied, the puréed form would seem to be the only one advisable for infant feeding, since it tends to increase rather than decrease the retention of iron and can be fed without harmful effects.

The effect of the apricots also appears to be negligible. They were fed only to infant No. 3. During the first of these periods the infant suffered from a respiratory infection which turned out to be very severe. Metabolism experiments with the apricots were continued after he had completely recovered. Whether this affected the iron metabolism during the apricot feeding or not it is impossible to say. The fact remains, however, that in only one of the three periods in which the diet was supplemented by apricots was there a positive retention, but this retention was large enough to increase slightly the average retention on a milk diet of +0.060 mg to +0.066 mg. This small effect would seem to be insignificant.

Hemoglobin determinations (Newcomer method) and red cell counts* were made at the end of each of the different diet periods as shown in Table I. Certainly the very small increases in retention

*We are indebted to Dr. Katsuji Kato for all of the hemoglobin determinations and red cell counts.

which occurred as a result of adding spinach or apricots to the milk diet were not accompanied by a rise in the hemoglobin or red cell count of the blood

In both infants, the pureed spinach periods were accompanied by a fall in hemoglobin concentration. The changes with the feeding of

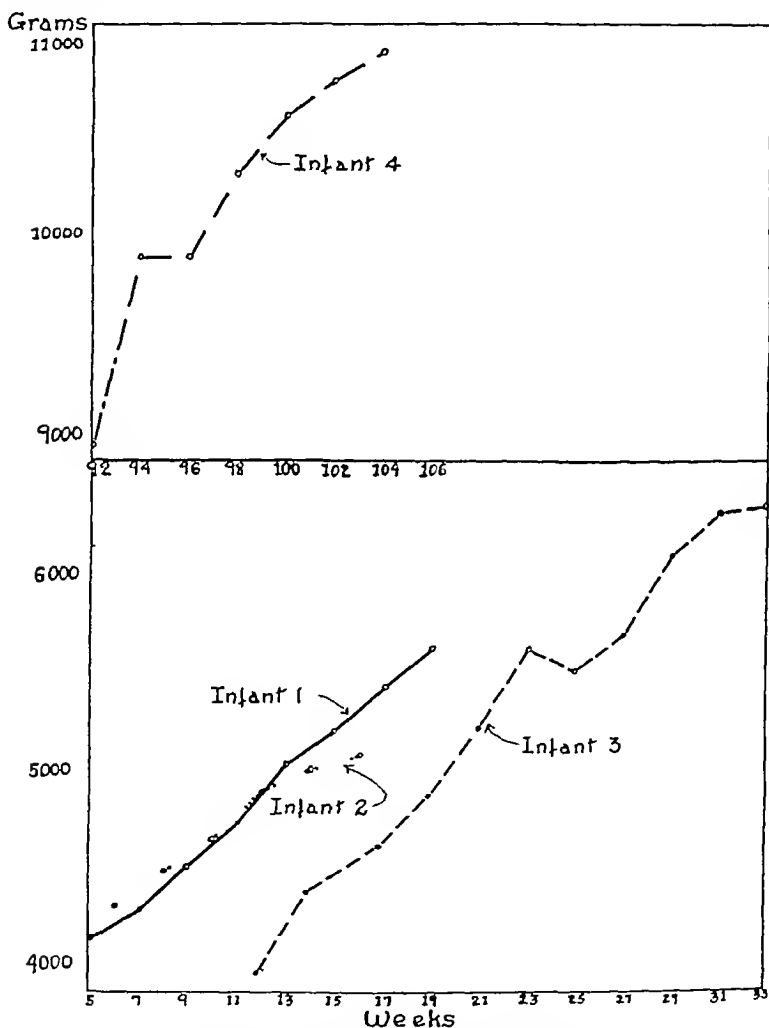


Fig 2—Showing the growth of the four infants whose iron metabolism was studied during the period they were under observation

raw spinach are contradictory. The low values in the later periods of infant No 3 are probably not effects of the apricot or dried spinach diet but are results of the respiratory infection. With the exception of the low hemoglobin values following an infection, all values for the three normal infants fall close to or above the average value found by Kato and Emery⁹ for infants in this vicinity. During the

time they were under our observation, they grew normally as shown in Fig 2. The average daily retention of iron for the three infants over the period studied was +0.08 mg.

We were able to test the effect of spinach and apricot feeding upon the iron metabolism of an anemic infant in whom there was a definite lack of hemoglobin, possibly a lack of iron because the infant would eat very little except milk. The infant was twenty three months old and weighed 9 kg. He was brought into the hospital with an acute upper respiratory infection which was soon cured. His diet, previous to the time he was admitted had consisted almost entirely of milk. As determined in the clinical laboratory, his hemoglobin was 37 per cent and red cell count 3,100,000.

The general plan of feeding follows: after a short control period on a milk and sugar diet with cod liver oil, dried spinach was added to the formula in two of the five daily feedings. This diet lasted about three weeks during which time two metabolism periods were carried out. The feeding of spinach was continued, but apricots were then also added to the diet in the remaining three feedings. A period of three weeks on the spinach apricot diet followed and again two metabolism periods were secured. Another similar three-week period followed in which the spinach apricot diet was supplemented by wheat germ extract, a potent source of vitamin B. A fourth three-week period studied the effect of a daily dose of 100 mg of iron as ferrous ammonium citrate accompanied by a trace of copper 0.75 mg in addition to the spinach apricot wheat germ diet. Finally the added effect of liver has been studied.

The results are shown in Table II and Fig 3. Weekly determinations of the hemoglobin concentrations and red cell count of the blood were made. Only those at the end of each diet period are given in the tables. The chart is drawn to the same scale as the one used for the normal infants but after iron salts were added the height of the columns became so great that they could not be represented in their entirety. The results of the iron balance are interesting but perplexing. The two metabolism periods on a given diet agree well with each other thus tending to give confidence in the results as they appear. The two periods in which the milk was supplemented by dried spinach gave one small positive balance followed by a negative balance. Certainly the added iron of the spinach was not being utilized. The output of feces during this period was considerably increased (an average daily output of 11.75 gm (measured in terms of dried weight) as compared with a preceding 6 gm daily output. When apricots were added the average daily output of feces was reduced to 8.37 gm. Correspondingly the output of iron was reduced and the iron balance became strongly positive showing an average retention of +2.97 mg Fe. Wheat germ extract was added at this point chiefly to com-

plete the infant's diet with an adequate source of vitamin B. After the addition of the wheat germ extract, the daily output of feces was 13.96 gm. Again the iron output increased and the iron retention was reduced to an average of +0.09 mg Fe.

The addition of soluble iron and copper salts to the diet resulted in a large increase in iron retention. This was not accompanied by a

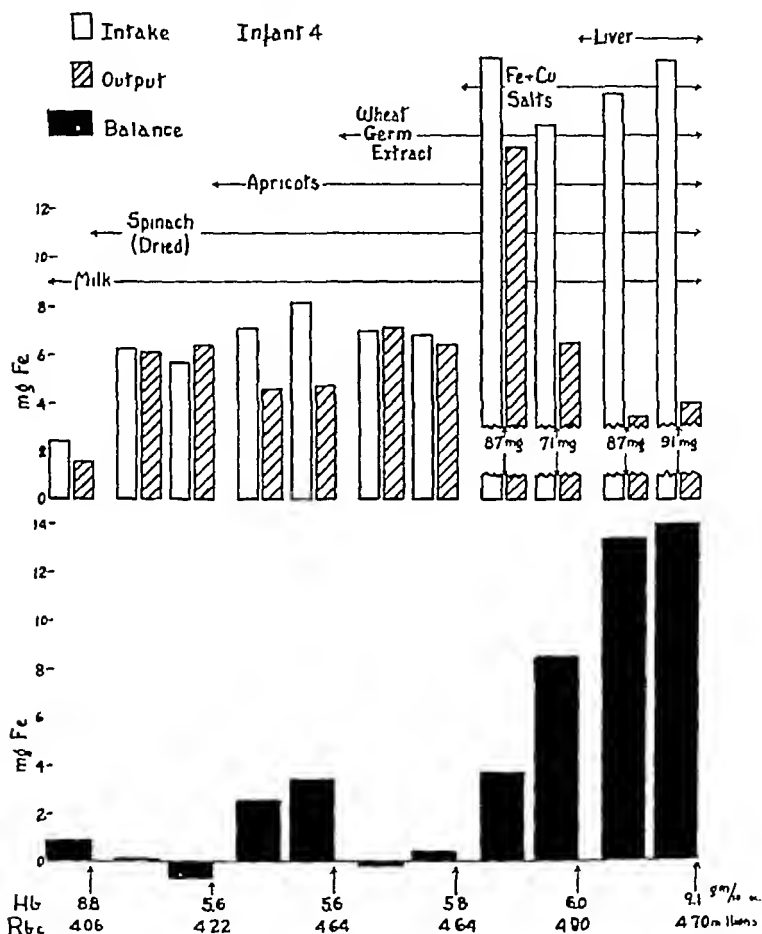


Fig 3—Showing the iron metabolism of an anemic infant as it was affected by various additions to the diet.

low output of feces, as was the case when a high retention occurred on a milk diet supplemented only by spinach and apricots. The results of these two last periods when soluble iron salts were given agree only fairly well with each other. In the last of the two periods, the intake and output of iron are both smaller, but not in the same proportion so that the retention is considerably greater. There was a smaller output of feces in this period and the increased retention might be explained by assuming that there was an incomplete

TABLE II
IRON METABOLISM OF AN ANEMIC INFANT AS INFLUENCED BY VARIOUS ADDITIONS TO THE DIET

PERIOD NO	NO DAYS IN PERIOD	NATURE OF SUPPLEMENT TO MILK DIET	HR	R.B.C. millions	WT OF DRIED FECES gm.	TOTAL FE INTAKE mg	FE IN FECES mg	FE IN URINE mg	FE BALANCE mg
1	4	0	gm. per 100 c.c. 38	4.00	0.00	2.42	1.54	0.021	+0.86
2	6	Spinach (dried)			11.50	6.21	0.07	0.024	+0.15
3	6	Spinach (dried)	56	4.22	11.92	5.72	6.34	0.029	-0.05
4	6	Spinach apricots			8.80	7.11	4.53	0.020	+2.55
5	6	Spinach, apricots	56	4.64	7.94	8.00	4.64	0.034	+3.39
6	6	Spinach apricots wheat germ			14.73	6.88	7.05	0.037	-0.21
7	5	Same as Period 6	53	4.00	17.21	0.78	6.35	0.041	+0.30
8	5	Spinach, apricots, wheat germ			13.08	10.19	60.40	0.045	+3.73
9	6	Fe and Cu salts							
10	3	Same as Period 8	60	4.90	0.44	84.03	75.5-	0.030	+8.47
		Spinach, apricots, wheat germ, Fe and Cu salts, liver			13.00	101.74	88.30	0.068	+13.37
11	5	Same as Period 10	61	4.70	12.84	107.09	93.05	0.042	+14.00

collection of feces. However, the following facts have to be critically considered. This last period was quite unsatisfactory because the infant exhibited an extreme loss of appetite. Some of the formula was refused and of that consumed, about 13 per cent was regurgitated. The amount of non refused could be determined accurately, but the amount regurgitated was estimated as explained earlier. However, since most of the formula refused contained only milk and spinach, the error introduced was small compared to the retention as calculated. On the other hand, the smaller food intake would account fairly well for the smaller output of feces. We feel, therefore, that the retentions as calculated represent, if not accurate values, at least the order of magnitude of the retention. With the additional feeding of liver, there was a further remarkable increase in the retention of iron although the iron content of the diet was scarcely affected by such feeding.

Examination of the hemoglobin concentrations and red cell count of the blood shows that very little improvement took place until liver was added to the diet. There was a gradual increase in the number of erythrocytes, from 4.06 to 4.90 million. The hemoglobin concentration fell sharply from an initial value of 8.8 gm per 100 cc to a minimum of 4.9 gm at the end of seven weeks. A week later it had returned to 5.6 gm. From that point on it remained fairly constant until the last week of the period during which soluble iron salts were given when it rose to 6.0 gm. Whether this meant that the hemoglobin concentration was beginning to increase and would continue so on the same level of iron and copper intake is not known. The feeding of liver was begun at this time and the hemoglobin rose to 9.8, a rise which was practically maintained during the second liver metabolism experiment.

DISCUSSION

The results reported here support the conclusion of earlier experiments that in the case of the normal infant the feeding of vegetables in the form of spinach does not appreciably affect its retention of iron. The same appears to be true of the feeding of fruit in the form of apricots. Whatever increases in the iron retention have resulted by feeding spinach or apricots have been small and apparently insignificant. There has been no increase in the hemoglobin concentration or the number of erythrocytes of the blood as the result of such feeding. On the contrary, there has been a tendency toward a decreased hemoglobin concentration.

The fact that two of the infants showed hemoglobin values considerably above the mean as determined by Kato and Emery³ for infants in this vicinity would indicate that they had as yet no iron need which was not met by their own reserves or by the iron sup

phed in the milk. There was usually a small retention of iron when the infant was on the ordinary milk formula, and this retention represented only a small proportion of the iron intake. The higher level of hemoglobin concentration for normal infants found by Mackay¹⁰ and Bloxson¹¹ as a result of iron or iron and copper medication does not necessarily conflict with our findings, since we have studied only three infants two of whom had unusually high hemoglobin concentration at the beginning of the metabolism experiments. Whether the high level of hemoglobin would have been maintained had the diet not been supplemented by iron-containing vegetable or fruits is a question for debate. At least, one can say that there was no indication of an appreciably increased iron retention as the result of such feeding which might favor the maintaining of this high level.

While the normal infant may not need a greater intake of iron up to the age of six months, another problem is presented in the case of an older infant who has been existing for many months almost exclusively on a milk diet. It is generally conceded that such an infant is not receiving enough iron to maintain the hemoglobin of the blood at its normal level and an anemia results. When such a case was admitted to the hospital we took the opportunity to determine whether the iron of spinach or apricots could be utilized by such an infant. It was impossible to study the problem rigidly in the one case. Other infants would have to be studied and the problem attacked from different angles. Even such a thing as the form of spinach used would have to be considered, because there seems to be evidence that the iron of dried spinach is not utilized so readily as that of puréed spinach. Our results, therefore, can only be considered with much reserve until more data are available.

In the case studied the iron of dried spinach was not utilized but that of the apricots was retained in considerable amounts. Coincident with this effect perhaps its cause, was a much smaller output of fecal matter after the milk-spinach formula was supplemented by apricots. No such phenomenon was observed when apricots were added to the milk formula of the normal infant. Again after adding wheat germ extract the output of feces increased and the iron retention fell to a low level. We are at a loss to explain such results without more data. The two periods on an identical diet agree well in each case. Whether this is an accident, and what we have observed is only a normal physiologic variation independent of the wheat germ could not be determined except by repetition of the experiments. For the present we prefer to put the results on record as those of an individual case only.

With the exception of the wheat germ effect, the results of apricot feeding on iron retention were what had been anticipated from the favorable results on hemoglobin regeneration which Whipple and

Robscheit-Robbins⁹ had found in the case of feeding apricots to their anemic dogs. On the other hand, we did not get an increased retention of iron with the feeding of dried spinach, such as Krasnorgorsky¹² found when the milk diet was supplemented with spinach extract and lactose. Possibly this is explained either by the fact that in the normal infant we found a better retention for pureed spinach than for dried spinach or by the fact that Krasnorgorsky's metabolism experiments lasted only three days, a period which is now considered inadequate for accurate results. Possibly another explanation is offered by the recent report of Schiff, Elhasberg and Joffe¹³ that when cow's milk was supplemented by lactose in the diet of rats an increase in hemoglobin concentration occurred.

The failure of our spinach or apricot feeding to produce a rise in hemoglobin concentration is contrary to the findings of many investigators, Hart, Steenbock, et al.,⁴ Whipple and Robscheit-Robbins,⁷ Mitchell and Vaughn,¹⁴ Sheets, Frazier, and Sulzby,¹⁵ Farmer and Cory,¹⁶ and Levine, Culp and Anderson,¹⁷ that the feeding of green-leaved vegetables or of some fruits, such as apricots, to anemic animals (dogs or rats) has resulted in an increase in hemoglobin level. In interpreting the results with the spinach or apricots, there must also be considered the fact that during the three weeks in which the iron of the diet was also supplemented by iron and copper salts in spite of a large iron retention there was no appreciable rise in the hemoglobin concentration of our infant, a result which was unexpected in view of the animal experiments of Hart, Steenbock and Elvehjem⁴ and the results of the use of iron and copper therapy for anemic infants and children by Josephs,¹⁸ Lewis,¹⁹ and Caldwell and Dennett.²⁰ Possibly we gave too small a dose of iron and copper. It increased the iron intake about twelve times over that in the milk-vegetable diet, but was considerably less than the dose used by Josephs. Perhaps we would have had better results with a larger amount of copper. It was believed unwise to increase the dose at the time because of the infant's tendency to vomit. We hope later to try out the effect of larger doses of both iron and copper.

The fact that the hemoglobin concentration finally rose almost to the normal level after liver was added to the diet is in agreement with the findings of Greengard, Maurer and Kluver²¹ in cases of infants whose anemic condition did not respond to iron treatment but who showed improvement after liver extract was also given. In this connection it should be remembered that these investigators found that liver extract alone caused an improvement in the blood picture in 63 per cent of the cases studied, and that in those cases which did not respond, improvement occurred after iron was added.

Favorable effects of the feeding of liver or liver extracts in cases of alimentary anemias of infancy have also been reported by Herz,²²

Tuscherer,²⁴ Ligum,²⁵ and Strunz.²⁶ We did not try the effect of liver alone. It was believed that the history of the case pointed definitely to a need for iron and that need was supplied by the spinach, apricots, and later, in a much more concentrated form, by the ferric ammonium citrate. The large retentions of iron, which occurred with the feeding of apricots and soluble iron salts, gave evidence that the iron need had been met. That no improvement occurred in the blood picture seemed to indicate the need of a supplementary factor to stimulate the hematopoietic functions to make use of the iron. According to the findings of Hart, Steinhock and Flvehjem and Peterson,²⁷ this should be copper.

Whether the increased hematopoietic activity which occurred during liver feeding was due to an increased copper intake or to the action of another supplementary factor in the liver cannot be determined from the data at hand. Another possible explanation might eliminate the liver entirely as a factor and assume that the results were simply a delayed effect of the iron and copper salts because the hematopoietic functions had been reduced in activity to such an extent and over such a length of time that a considerable latent period might be required before stimulation would have its effect. Further experiments along this line are planned. For the present we can only say that the increased iron retentions in an anemic infant which were found as a result of the feeding of apricots and to a greater extent with the administering of iron and copper salts, were not immediately reflected in an improved blood picture. There was a later increase in hemoglobin concentration which might have been due either to a delayed effect of the increased iron and copper intake or to some factor in the liver which was finally included in the dietary.

SUMMARY

1. A study of the iron metabolism of three normal infants, ranging in age from five weeks to seven months, has shown that vegetable (spinach) or fruit (apricots) feeding in addition to the milk formula exerts no significant effect upon the amount of iron retained by the infant. Such feeding increased the iron intake 60 to 171 per cent. The hemoglobin concentration and the number of erythrocytes in the blood were within or above the normal range for infants of this vicinity and age and were not raised by the vegetable or fruit feeding.

2. A study of the effect of such feeding upon an anemic infant, twenty-three months old who had been living on an almost exclusive milk diet, has shown a lack of effect in the case of dried spinach, but a marked increase in retention of iron when apricots were added to the diet, an effect which disappeared again after wheat germ extract was also included. The effect in each case is related to the amount of

fecal matter eliminated in the metabolism period. We prefer to withhold interpretation until more data are available. The hemoglobin concentration and erythrocyte count of the blood were not improved during the course of such feeding.

3 A very large increase in the concentration of soluble iron in the diet of the anemic infant, brought about by adding ferric ammonium citrate, resulted in a large increased retention of iron, but up to the end of three weeks on the diet, only a very slight increase in the number of erythrocytes had occurred and practically no change in hemoglobin concentration.

4 When the diet of the anemic infant was further supplemented by liver, the retention of iron was increased still more. The retention in this instance was accompanied by a rise in hemoglobin from 60 to 91.

REFERENCES

- 1 Bunge, G. von. *Ztschr. f. Physiol. Chem.* 13: 399, 1889. *Ibid.* 16: 173, 1892.
- 2 Hugounenq, M. L. *Compt. rend. Acad. d. sc. des Paris* 128: 1054, 1899. *Ibid.* 130: 1422, 1900. *J. de physiol. et de path. gén.* 1: 703, 1899. *Ibid.* 2: 1509, 1900.
- 3 Czerny, A., and Keller, A. *Des Kindes Ernährung und Ernährungs Störungen*, ed. 2, Leipzig and Vienna, 1928, F. Deuticke.
- 4 Hart, E. B., Steenbock, H., Elvehjem, C. A., and Waddell, J. *J. Biol. Chem.* 65: 67, 1925.
Hart, E. B., Elvehjem, C. A., Waddell, J., and Herrin, R. C. *J. Biol. Chem.* 72: 299, 1927.
Waddell, J., Elvehjem, C. A., Steenbock, H., and Hart, E. B. *J. Biol. Chem.* 77: 777, 1928.
Hart, E. B., Steenbock, H., Waddell, J., and Elvehjem, C. A. *J. Biol. Chem.* 77: 797, 1928.
Waddell, J., Steenbock, H., and Hart, E. B. *J. Biol. Chem.* 83: 243, 1929.
- 5 Whipple, G. H., and Robscheit Robbins, F. S. *Am. J. Physiol.* 72: 408, 431, 1925.
Robscheit Robbins, F. S., and Whipple, G. H. *Am. J. Physiol.* 79: 271, 1927. *Ibid.* 80: 400, 1927. *Ibid.* 83: 76, 1927.
Robscheit Robbins, F. S., Elden, C. A., Sperry, W. M., and Whipple, G. H. *J. Biol. Chem.* 79: 563, 1928.
Elden, C. A., Sperry, W. M., Robscheit Robbins, F. S., and Whipple, G. H. *J. Biol. Chem.* 79: 577, 1928.
Whipple, G. H. *J. A. M. A.* 91: 863, 1928.
Whipple, G. H., and Robscheit Robbins, F. S. *Am. J. Physiol.* 92: 362, 388, 1930.
Robscheit Robbins, F. S., and Whipple, G. H. *Am. J. Physiol.* 92: 400, 1930.
- 6 Minot, G. R. *Tr. Coll. Physicians* 49: 144, 1927.
Minot, G. R., Murphy, W. P., Cohn, E. J., Stetson, R. P., and Lawson, H. A. *Tr. A. Am. Physicians* 42: 83, 1927.
Minot, G. R., Murphy, W. P., and Stetson, R. P. *Am. J. M. Sc.* 175: 581, 1928.
Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A. *Am. J. M. Sc.* 175: 599, 1928.
Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T. *J. B. C.* 77: 325, 1928.
Minot, G. R., Murphy, W. P., and Cohn, E. J. *Ann. de Med.* 23: 319, 1928.
Minot, G. R., and Castle, W. B. *Ann. Int. Med.* 5: 159, 1931.
Minot, G. R., and Heath, C. W. *Tr. A. Am. Physicians* 46: 290, 1931.
- 7 Schlutz, F. W., and Morse, M. *Am. J. Dis. Child.* (In press.)
- 8 Stugart, R. *Ind. and Eng. Chem. Analytical Edition* 3: 390, 1931.
- 9 Kato, K., and Emery, O. J. *Folia Haematol.* 49: 106, 1933.

- 10 Mackay, H. M. Medical Research Council, Report No. 157, London 1931
- 11 Blossom, A. P. Southern M. J. 25 401 1931
- 12 Krasnorgorsky, N. Jahrb. f. Kinderh. 64 631 1900
- 13 Schiff, E., Ellasberg, H., and Joffe, N. Jahrb. f. Kinderh. 139 143, 1933
- 14 Mitchell, H. and Vaughn, M. J. Biol. Chem. 75 127 1927
- 15 Sheets, O., Frazier, F., and Gulick, A. Mass. Sta. Rpt. 23, 1930
- 16 Farmer, C. J., and Corv, E. E. Proc. Soc. Exper. Biol. & Med. 29 780 1931
- 17 Levine, H. Culp, F., and Anderson, O. J. Nutrition 5 295 1932
- 18 Josephs, H. W. Bull. Johns Hopkins Hosp. 49 246, 1931
- 19 Lewis, M. S. J. A. M. A. 98 1175, 1931
- 20 Caldwell, G. W., and Dennett, R. H. Med. J. & Rec. 135 286, 1932
- 21 Maurer, S., Greengard, J., and Klüber, C. J. A. M. A. 98 1069, 1932
- 22 Greengard, J. J. Am. Diet. Assn. 8 33 1932
- 23 Herz, O. Monatschr. f. Kinderh. 40 116, 1928
- 24 Tauscherer, J. Monatschr. f. Kinderh. 39 201 1928
- 25 Ligum, J. Monatschr. f. Kinderh. 43 517, 1929
- 26 Strunz, F. Arch. f. Kinderh. 95 98 1931
- 27 Lindow, C. W., Elvehjem, C. A., and Peterson, W. H. J. Biol. Chem. 82 405 1929

CHOLESTEROL PARTITIONS OF THE BLOOD IN MYXEDEMA (CRETINISM)

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IT IS known that disturbances of the thyroid gland are associated with a disturbed cholesterol metabolism. The total amount of cholesterol in the blood is normally from 100 to 230 milligrams in 100 c c¹. In both clinical and experimental hyperthyroidism² the blood cholesterol tends to be reduced. In hypothyroid states the total blood cholesterol tends to be increased.³

Because of this association, Epstein and Lande⁴ studied the level of the blood cholesterol and the level of the basal metabolic rate. They found an inverse ratio of the basal metabolism and the blood cholesterol which they explained on the basis of an increased rate of oxidation. This caused increased consumption of available lipid with reduction in the blood and vice versa.

In general, we may say that there seems to be a fairly definite relationship between the basal metabolic rate and the cholesterol level of the blood in myxedema. In untreated myxedema, the cholesterol is increased and the basal metabolism is decreased. As the basal metabolic rate is raised by thyroid therapy, the blood cholesterol is lowered. We were able to observe a case of a twelve-year-old untreated cretin in our wards who illustrated the almost mathematical relationship between basal metabolism and blood cholesterol. Fig 1 shows graphically what occurred with thyroid therapy.

In nephrosis the blood cholesterol is usually increased. The subnormal basal metabolism, when it occurs, is probably not due to hypothyroidism, but perhaps to defective protein metabolism. However, even in nephrosis, Epstein and Lande⁴ found a similar inverse relationship between basal metabolic rate and blood cholesterol level, as both were influenced by thyroid therapy. We were able to study a group of cases of nephrosis in children between the ages of two and ten years. We may say that in our cases fluctuations in the level of the blood cholesterol were quite independent of thyroid therapy. There seemed to be no constant relation between the level of the blood cholesterol and the basal metabolism. From our experience therefore, we can corroborate the findings of Epstein and Lande in so far as myxedema of endocrine origin is concerned, but not for nephrosis.

From the Wards of the Pediatric Department and the Laboratories of The Mount Sinai Hospital, New York.

Cholesterol appears in the blood uncombined or as free cholesterol, and as cholesterol ester. The relative proportion is free 20 to 50 per cent, ester 50 to 80 per cent. This relationship normally is quite constant regardless of the total amount of cholesterol present. In pregnancy Bloor and Knudson⁶ find a relative increase in the ester and Knudson⁶ says there is also an increase in ester after feeding a high fat diet. In cases of mechanical icterus, the cholesterol ester is often diminished.⁷ Thannhauser⁸ showed that in conditions of liver atrophy there is a decrease of ester, which may go on to a complete disappearance. This has been verified by F. Z. Epstein.⁹

BASAL METABOLIC
RATE

CHOLESTEROL
MILLIGRAMS

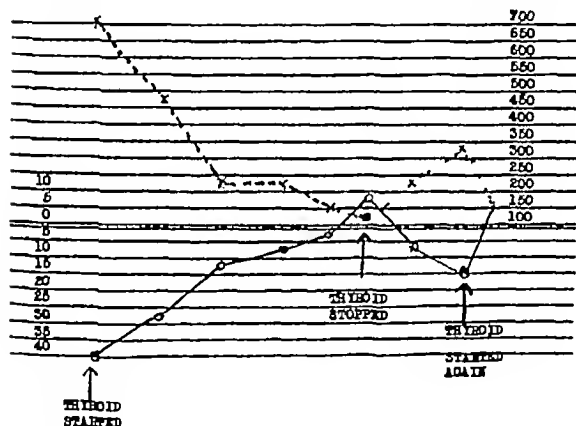


Chart I—Relationship of cholesterol level to basal metabolic rate under thyroid therapy in cretin (Case 5)

Table I shows the cholesterol determinations in a case of subacute yellow atrophy of the liver studied on our wards, which corroborates Thannhauser's and Epstein's findings.

TABLE I

DATE	TOTAL CHOLESTEROL	ESTER	FREE	REMARKS
Oct. 31, 1931	187	82	105	H G a girl 8 years old
Nov. 14	198	29	169	
Jan. 4 1932	116	faint trace	115	
Feb. 15	100	19	81	
Mar. 4	80	faint trace	80	

Postmortem findings showed complete destruction of normal lobular markings of the liver

Liver damage, we believe is the only known condition in which the ester concentration in the blood stream is markedly decreased

In studying the cholesterol of the cretin cited above, we found such a marked diminution in the ester of the blood, especially in relation to the free cholesterol, that the ratio usually found in the normal between ester and free cholesterol was reversed. In order to determine whether this was an accidental finding or whether there is actually a decrease in the ester in the blood in myxedema of childhood, we studied the blood cholesterol partitions of eleven cases of myxedema (cretinism). The findings are given in Table II.

TABLE II

CASE	AGE	SEX	TOTAL CHOLESTEROL	ESTER	FREE	B M R *	ESTER %	REMARKS	THYROID THERAPY
1	5 years	♂	470	210	260	minus 2%	44%	treated since 2½ years of age	
2	4 years	♂	210	90	120	not done	43%	treated since 2½ years of age	
3	9 years	♂	190	75	115	plus 3%	38%	treated since infancy	
4	11 years	♀	250	95	155	plus 1%	38%	treated since 5 months old	
5	12 years	♀	676	270	406	minus 39%	20%	untreated Feb 13/31	
			120	70	50	plus 8%	58%	treated March 17/31	
6	17 years	♀	170	100	70	plus 9%	58%	treated since 2 months old	
7	8 years	♀	290	135	155	minus 19%	48%	treated on and off since 8 months of age	
8	4 years	♀	320	90	230	minus 19%	28%	myxedema developed at age of 2, untreated	
9	6 years	♀	215	86	129	not done	40%	treated since early childhood	
10	13 years	♀	340	195	145	not done	57%	treated since childhood	
			300	200	100		66%		
11	6 years	♀	200	100	70	not done	50%	treated since early childhood	

Male ♂ Female ♀

*The basal metabolic rate was charted against total calories referred to age—a standard which Talbot considers the best for cretins in judging effect of thyroid therapy.

It will be seen from columns 3 and 4, that instead of the normal ratio of 50 to 80 per cent there is frequently a decrease, so that there is less ester than free cholesterol. This was noted in all cases except Cases 5, 6, 10 and 11.

After intensive treatment with thyroid, Cases 5 and 6 had a fairly high basal metabolism, quite normal however, for their age, as the basal metabolism in childhood tends to be high and the ratio ester to free was normal. It is possible that the determination of the cholesterol fraction is of value in the progress of the therapy, and that this figure in conjunction with the basal metabolic rate may be an aid in judging the result of treatment. At this time we shall not enter into an explanation of the ester.

tainly not lay the decrease to some dysfunction of the liver. Rather we quote Thannhauser,¹⁰ "In atrophy of the liver the total cholesterol in the blood is reduced and the ester is almost absent. Diametrically opposed to this we have shown, that in animals in whom the liver has been removed, the total cholesterol in the blood is increased, especially the ester portion. The liver may be responsible for the ratio cholesterol ester to free cholesterol in the blood." At present therefore this statement expresses very concretely the extent of our knowledge of cholesterol in the blood which we hope may be enlarged by the investigation of more material, especially in untreated or poorly treated cretins.

SUMMARY AND CONCLUSIONS

In myxedema of hypothyroid origin, there is a very definite inverse relationship between the total cholesterol level and the level of the basal metabolic rate, the cholesterol is high the basal metabolism low. When thyroid extracts are administered, the basal metabolic rate rises, and the level of the total cholesterol simultaneously falls to normal (below 250 mg). In nephrosis, although the total cholesterol is increased, and the basal metabolism may be decreased, there is no constant relationship between the two, nor is there any predictable effect of thyroid therapy.

Cholesterol appears in the blood in the free state and as cholesterol ester the relative proportion being—free, 20 to 50 per cent, ester, 50 to 80 per cent.

The only known pathologic condition in which the relative proportion is reversed is liver atrophy, in which condition there is a decrease of ester, which may go on to almost complete disappearance.

This paper reports the results of a study of the proportion of free cholesterol to ester in 11 cases of myxedema of hypothyroid origin. In all but four of the cases the ester was reduced, so that the normal ratio of combined (ester) to free cholesterol was reversed—a reversal which as far as we could ascertain from the literature occurs only in hepatic dysfunction. In these four cases the lowest figures in the group for total cholesterol was obtained, and the ratio of ester to free cholesterol was normal—they also had the highest basal metabolism in the series—perhaps the most normal for the age as the basal metabolism in childhood tends to be rather high than low.

It seems that in myxedema of childhood (cretinism), not only is the total cholesterol increased but at times the ratio of ester to free cholesterol is disturbed, so that the relative proportion is reversed. This ratio may become normal after intensive treatment with thyroid extracts.

It is possible that in the determination of the ester to free cholesterol ratio we may have a valuable diagnostic aid to thyroid therapy in this condition.

REFERENCES

- 1 Gardner and Gainsborough Biochem J 19 667, 1925
Campbell, J M H Quart J Med 18 393, 1925
- 2 Bing and Heckscher Biochem Ztschr 144 83, 1924 Ibid 158 403, 1924
Gardner and Gainsborough Brit M J 5 935, 1928
- 3 Heckscher Biochem Ztschr 158 417, 1925
Wade Am J M Sc. 177 790, 1929
Denis, W J Biol Chem 29 93, 1917
Baumann and Holly Am J Physicians 75 618, 1926
Parhon and Derivici Compt rend Soc de Biol 95 787, 1926
- 4 Epstein and Lande Arch Int Med 30 563, 1922
- 5 Bloor and Knudson J Biol Chem 27 107, 1916
- 6 Knudson J Biol Chem 32 337, 1917
- 7 Burger, M Verhandl d deut ges f inn Med, 1931, p 186
- 8 Thannhauser, S J Klin. Wchnschr 12 53, 1933
- 9 Epstein, E Z Arch Int Med 47 82, 1931 Ibid 50 203, 1932
- 10 Thannhauser, S J Klin Wchnschr 12 49, 1933

INTERPRETATION OF BASAL METABOLISM OF CHILDREN

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THE portable metabolism apparatus which was hardly seen outside of hospitals a dozen years ago, is now frequently included in the office equipment of physicians in many parts of the country. This means that metabolism determinations, which at first could be made only by a few specially trained investigators, can now be included in most clinical studies of obscure disease. The purposes of this paper are to summarize the knowledge required for clinical metabolic tests and to indicate in so far as possible the errors to be guarded against in obtaining and interpreting metabolic data. Although many of the factors to be mentioned are significant in studying the basal metabolism of adults, they are here considered chiefly from the pediatrician's viewpoint.

The methods of obtaining metabolism measurements fall into two categories—the indirect and the direct. When the indirect method is used, the amount of heat produced by the patient in a given length of time is not determined *per se*, but is calculated from measurements of the oxygen consumption. The direct method involves measurement of the heat production itself. For this direct calorimetry, the patient must be placed in a closed chamber equipped with suitable recording mechanisms. This is the more comfortable method for the patient, but it requires apparatus not available to the practitioner in most places. The discomforts involved in indirect measurement of the heat production (portable apparatus) are not severe and cause relatively little disturbance of physiologic conditions once the patient has become accustomed to them. The patient lies quietly on a couch for a brief period breathing through a rubber mouthpiece connected with the oxygen supply and recording apparatus. Nose breathing is prevented by a clip. The test is easily performed and the technique can be learned in a short time by any one accustomed to simple laboratory procedures. If directions are followed accurately, there is little chance of introducing errors other than those inherent in the method itself.

The majority of inaccuracies are due to failure to establish "basal conditions" before and during periods of observation. Lack of cooperation, and the excitement or nervousness of the patient due to fear or unfamiliarity with test conditions during the first observations and nervousness and lack of tact on the operator's part are the most frequent causes of unsatisfactory measurement. Work with children requires special knowledge and experience as well as the even temperament and easy manner which inspire confidence. Without

these, measurement is impossible, for true "basal conditions" cannot be established or maintained during the period of observations unless the child is essentially contented. Basal figures can rarely be obtained from children during the first test period because of lack of adjustment to the necessary conditions. Frequently, it is impossible to get significant data on the first day that the child is tested. Readings should not be considered basal unless those taken during two periods agree within 4 per cent. Satisfactory figures can rarely be obtained by means of the portable apparatus from children less than eight years old.

Individual measurements are of little significance, of course, unless compared with a definite standard. The methods by which the various available tables have been compiled should be thoroughly understood before results are interpreted, if conclusions are to be valid. No figures should be blindly accepted at face value, for the effect of certain important factors cannot be included in the standard tables. In the tables constructed from the findings of Benedict and Talbot, the figures given for children less than two years of age are not strictly comparable with those for older children because they were obtained shortly after the babies had been fed. They do, however, fulfill all other requirements of basality and therefore constitute a suitable basis for comparison. The data for children less than eight years old were obtained in the cot-chamber, those for older children by the portable apparatus in most instances.

The standards for metabolism, like those for height and weight, are average figures. Since they are not absolute, it must always be remembered that the limits of normal lie above and below the figure given. In adults, normal variations may amount to as much as 10 per cent in either direction, in children, interpretation is more difficult because a larger proportion of measurements falls outside these limits, the proportion decreasing with age. More care is therefore necessary in the interpretation of slight deviations in young patients.

The fact is now generally accepted that the amount of heat produced depends upon the amount of active protoplasmic tissue in the body, that is, for the most part upon the size of the muscles and internal organs. Inactive tissues like bone, fat, and the body fluids do not produce heat. Since the relative proportion of active and inactive tissue in the body varies greatly with different individuals, and may vary considerably in any one individual at different times, figures obtained from metabolic studies may at first glance appear misleading. Interpretations consistent with clinical experience can be made only after the ratio between the two types of tissue has been estimated. Metabolic data obtained from children of average normal development that is whose weight corresponds closely to the average for height and sex, can be compared satisfactorily with all available

standards (calories per square meter of body surface, calories per kilogram of body weight, total calories for age, total calories for height, total calories for weight) Metabolic data from thin or fat children, on the other hand, must be interpreted with care, for the make up of the body has a great effect upon the significance of the figures Unless weight is approximately average for height and sex, metabolic data cannot be compared with any standard in which total heat production is divided by the weight—alone or as part of some formula, for example, with tables of the average number of calories per kilogram of body weight or of the number of calories produced per square meter of body surface In the latter case, the surface area of the body is estimated from a formula which includes weight It is possible partly to compensate for errors which arise in this manner by making certain corrections, but in actual practice it is more satisfactory to compare the data obtained from fat or thin children with both weight and height tables (see Tables I and II) and to estimate the significance of the figures from the discrepancy between the two standards There is no standard of metabolism from which to draw conclusions about individual measurements with mathematical accuracy, because of the great variety of factors involved No table can be constructed to take all of these into account, but all factors should be considered in the diagnosis of each individual

Measurements obtained from tall and short children of average weight for height are comparable with standards of calories per square meter, calories per kilo, and total calories for height and weight Figures from underweight children are comparable with total calories for height, total calories for expected weight, calories per kilo of expected weight and calories per square meter of body surface if the expected weight and not the actual weight is used in the formula for figuring area of body surface If the actual weight is used in the last two calculations, the metabolism will appear increased, although it actually is normal in terms of total calories for height The metabolism of children who are obese (i.e., weigh 20 per cent or more above the average for children of the same height) shows the opposite effect until the extra activity involved in carrying the fat causes superior development of the muscles The calories per square meter and per kilo tend to fall below normal, and the total calories for height and for weight are normal After superior muscular development takes place, the metabolic figures are higher than the standard total calories for height and correspond closely to the total calories for weight The same effects may be seen whenever weight is added to the body in the form of inactive substance, for instance in edema and ascites

Table III gives an indication of the importance that may be attributed to percentage deviations from the standard metabolism when

TABLE I

BASAL 24 HOUR HEAT PRODUCTION OF BOYS AND GIRLS FROM THE FIRST WEEK AFTER BIRTH TO 12 YEARS OF AGE, PREDICTED FROM HEIGHT*

HEIGHT	PREDICTED HEAT		HEIGHT	PREDICTED HEAT	
	BOYS	GIRLS		BOYS	GIRLS
<i>cm</i>	<i>cal</i>	<i>cal</i>	<i>cm</i>	<i>cal</i>	<i>cal</i>
48	---	122	100	775	675
49	---	136	101	785	685
50	---	150	102	790	693
51	160	165	103	795	700
52	170	178	104	800	711
53	185	194	105	805	720
54	198	208	106	810	730
55	210	222	107	815	740
56	225	236	108	820	749
57	238	250	109	825	759
58	260	268	110	830	769
59	280	283	111	840	778
60	300	300	112	850	788
61	310	318	113	855	797
62	315	332	114	865	807
63	330	350	115	875	817
64	358	367	116	885	828
65	384	384	117	895	837
66	390	401	118	910	847
67	400	418	119	920	857
68	420	435	120	935	866
69	435	452	121	945	875
70	450	468	122	955	885
71	465	483	123	965	894
72	480	500	124	980	904
73	495	516	125	990	915
74	510	530	126	1000	925
75	525	543	127	1015	935
76	535	557	128	1025	945
77	555	567	129	1035	956
78	565	575	130	1045	965
79	577	583	131	1060	975
80	590	586	132	1072	985
81	600	591	133	1083	995
82	612	595	134	1095	1005
83	622	598	135	1105	1016
84	635	602	136	1115	1026
85	645	605	137	1130	1037
86	660	607	138	1140	1047
87	670	610	139	1152	----
88	685	612	140	1165	----
89	695	615	141	1175	----
90	705	617	142	1187	----
91	715	620	143	1200	----
92	725	623	144	1210	----
93	730	626	145	1220	----
94	740	630	146	1232	----
95	745	637	147	1242	----
96	755	644	148	1255	----
97	760	651	149	1268	----
98	765	659	150	1280	----
99	770	667	---	----	----

*Talbot F B Physiological Reviews 5 No 4 pp 490 491 October 1923

compared in the manner suggested above. In Table IV are listed a few conditions in which the metabolic level is of special interest.

It is technically easy to determine the metabolic level, often difficult to establish and maintain basal conditions, particularly in chil-

TABLE II

BASAL HEAT PRODUCTION OF BOYS AND GIRLS PER 24 HOURS PREDICTED FROM BODY WEIGHT

BODY WEIGHT (WITHOUT CLOTHING)	PREDICTED HEAT		BODY WEIGHT (WITHOUT CLOTHING)	PREDICTED HEAT		BODY WEIGHT (WITHOUT CLOTHING)	PREDICTED HEAT		BODY WEIGHT (WITHOUT CLOTHING)	PREDICTED HEAT	
	BOYS	GIRLS		BOYS	GIRLS		BOYS	GIRLS		BOYS	GIRLS
kilos	cal.	cal.	kilos	cal.	cal.	kilos	cal.	cal.	kilos	cal.	cal.
2.5	115	110	11.5	607	605	20.5	878	818	20.5	1103	1032
3.0	150	150	12.0	625	610	21.0	885	830	30.0	1115	1045
3.5	180	185	12.5	643	625	21.5	898	842	30.5	1127	1058
4.0	210	220	13.0	660	640	22.0	919	855	31.0	1140	1070
4.5	240	233	13.5	678	652	22.5	925	867	31.5	1159	1089
5.0	270	285	14.0	695	665	23.0	940	880	32.0	1160	1090
5.5	300	313	14.5	710	678	23.5	953	890	32.5	1170	
6.0	330	350	15.0	725	690	24.0	965	900	33.0	1189	
6.5	360	377	15.5	740	700	24.5	978	915	33.5	1199	
7.0	390	405	16.0	756	710	25.0	990	930	34.0	1200	
7.5	418	432	16.5	768	722	25.5	1005	940	34.5	1210	
8.0	445	460	17.0	780	735	26.0	1020	950	35.0	1220	
8.5	470	480	17.5	793	747	26.5	1033	962	35.5	1230	
9.0	495	500	18.0	805	760	27.0	1045	975	36.0	1240	
9.5	520	520	18.5	818	770	27.5	1058	987	36.5	1248	
10.0	545	540	19.0	830	780	28.0	1070	1000	37.0	1255	
10.5	568	560	19.5	845	793	28.5	1080	1010	37.5	1265	
11.0	590	580	20.0	860	805	29.0	1090	1020	38.0	1275	

From Benedict and Talbot. Carnegie Inst. Wash., Publication 30., p. 66.

TABLE III

+ 30 -----	High—if basal—except at puberty	} Only figures which have been obtained from repeated tests and have checked closely should be accepted as basal.
+ 20 -----	} Under suspicion	
+ 10 -----		
0 -----	Normal	
- 10 -----	} Under suspicion	
- 15 -----		
- 20 -----	Low	

TABLE IV

CONDITIONS IN WHICH THE METABOLIC LEVEL IS OF INTEREST

METABOLIC LEVEL		
DEPRESSED	NORMAL	ELEVATED
Subnormal temperature	Edema	Fever
Severe chronic malnutrition	Mongolianism	Hyperthyroidism
Hypothyroidism (myxedema)	(usually)	
Hypoadrenallism (Addison's disease)	Eczema (usually)	
Hypogonadism (probably)	Ichthyosis (usually)	
Mongolianism (occasionally)		
Eczema (occasionally)		
Ichthyosis (occasionally)		

dren, and always very difficult to interpret intelligently the figures obtained without knowledge of all the technical and physiologic factors which affect the significance of the standards

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77	555	567	129	1035	956
78	565	575	130	1045	965
79	577	583	131	1060	975
80	590	586	132	1072	985
81	600	591	133	1083	995
82	612	595	134	1095	1005
83	622	598	135	1105	1016
84	635	602	136	1115	1026
85	645	605	137	1130	1037
86	660	607	138	1140	1047
87	670	610	139	1152	----
88	685	612	140	1165	----
89	695	615	141	1175	----
90	705	617	142	1187	----
91	715	620	143	1200	----
92	725	623	144	1210	----
93	730	626	145	1220	----
94	740	630	146	1232	----
95	745	637	147	1242	----
96	755	644	148	1255	----
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compared in the manner suggested above In Table IV are listed a few conditions in which the metabolic level is of special interest

It is technically easy to determine the metabolic level, often difficult to establish and maintain basal conditions, particularly in chil-

regulation which intrauterine life characteristically provides. How often for example, does a premature infant of 1000 gm double its weight in the succeeding forty four days to keep the pace of more fortunate fetal contemporaries? Here indeed, we may truly say, is real growth but since it is rarely attained in a similar case under ordinary conditions of actual practice we are bound to inquire into the problem and the more so, when we compare the beautiful uniformity of data displaying the course of normal fetal growth with the vastly different and highly irregular trends commonly witnessed during corresponding intervals of postnatal existence.

Clinical interest in the matter of growth takes its origin most conveniently at birth. Among questions relating to growth and having considerable clinical importance even at this early stage of life are those regarding the viability and as already noted the development of the premature baby the cause of birth, and the physiologic loss in weight but their discussion must wait consideration of somewhat more fundamental problems.

Succeeding birth, we are wont to observe a young subject develop as the process of growth unfolds itself, and always to do so no doubt with a considerate and humble amazement at the regularity, and one may even add at the biologic precision with which the familiar landmarks are reached and passed. What, we ask, can this be, or failing the ultimate answer, what are the significant features of the process, how are they to be recognized or interpreted and what must be done to preserve them? We ask also that the answers be simple else our new knowledge can hardly have practical worth. But to insist on the latter stipulation, we imply *a priori* that the laws of growth are themselves simple and of this there is much legitimate doubt. We shall not, moreover, be spared a certain disappointment if we cannot at once accept the fundamental tenet that we deal in any form of growth, with one of nature's most complex mysteries. In fact it is easy to reach such a conclusion by examining a few elementary propositions.

REMARKS AS TO THE SIMPLICITY OF THE LAWS OF GROWTH

From the biologic point of view all growth is truly a matter of cellular multiplication. Let us set down then the simplest possible law of growth which with certain reservations, is this: *Cellular reduplication, once initiated, will continue uniformly in its state of motion until acted upon to change that state.* But in so doing we have already made three important assumptions regarding the nature of growth: first that growth consists of an increase in cell number, second that there exists something which will enable cells to reduplicate and third that there is something else which may or may not inhibit the process. A more complete statement, consequently would

require additional investigation into and specification of, each of these three postulates, to say nothing of an examination of the rather evident implication that growth once initiated will proceed, *other things being equal*, in purely geometric fashion

Now, it happens that the geometric type of reduplication is repeatedly approximated in every bacterial culture, that it is witnessed unequivocally in successive generations of paramecia, or in tissue-cultures, and that it even appears to quite a recognizable extent during the embryonic phase of human growth. But it is in this sense, and only in this sense that the law or its application remains "simple", for experience shows, as even Lucretius¹ knew, that reduplication under ordinary conditions of life comes sooner or later to a close. Our lines of inquiry must therefore be directed at the agencies which can and do affect the state of growth, as well as into those "things" which cannot now obviously remain "equal." Yet even if these circumstances may ultimately prove to be themselves of quite a simple nature (though this is also highly unlikely), we have departed from the simple to deal actually with something definitely complex. Nor is this all, for we have thus far just mentioned the matter of growth initiation, but not how this may be presumed in simple fashion to come about. Still, our main object of the moment has been achieved, for it is now evident that, if we seek and later obtain rudimentary relationships, we shall be able to deal only with rudimentary events, that the laws of growth, instead of being themselves simple, must clearly be organized combinations of more elementary statements, and finally that rugged simplicity in the case of human growth is beyond the range of expectation.

The preceding remarks are not intended to mean that the problem is any less soluble than before. Indeed, the reverse is actually true, for, as a result of all the work done previously, we are in better position than ever to recognize and to proceed with further projects. Modern knowledge of infant feeding with its heritage of the past has made us all familiar with the energy requirements of growing children. Studies of nutrition during the last quarter of a century, so ably presented and interpreted by Czerny in his classical work on the subject, have placed at our disposal a myriad of facts of everyday use, albeit that much of this information on growth has been collected, interestingly enough, through observations of the very process whose fundamental nature still remains obscure. Thus the indispensability of tryptophane, or of other amino acids, the similar and equally important need for the vitamins have in great part been established by observations which compared growth in the experimental animals with that in appropriate controls. Such studies are, however, more properly concerned in the last analysis with the fuel of growth rather than with growth itself. Still, on the basis of this vast and

solid foundation there can be no hesitancy today in accepting the view that all growth depends directly upon a suitable source of nutriment, and hence, in Spencer's terms, upon energy exchange as well.

In addition to this knowledge of fuel intake we possess reliable, though perhaps not complete, information on energy, or better, heat elimination. We know further, much about the natural course of growth, as this is recorded by incremental change from time to time. We need next a glimpse of what goes on in conjunction with and at the time of reduplication. From the dynamical point of view nothing would serve so well as some convenient measure of energy exchange, provided we knew the relation between growth on the one hand and say heat production on the other. Until recently no such direct relationship has been brought forward, our own results, elsewhere presented,² affording, we believe, some insight into the connections between growth and basal metabolism. It should, therefore, ultimately be possible to consider some of the underlying events as well as their clinical significance from each of these essentially practical points of view. Here, however it will be best to devote some preliminary attention to definitions especially to that of growth itself, to a consideration of the matter of size, as regards mass or length, and finally to a brief description of the scheme of energy exchange upon which the dynamical connection of growth and metabolism has been found to depend.

DEFINITIONS

In treating the problem of growth primarily from the clinical point of view it is comparatively easy to set down and to accept almost any of the definitions of growth thus far proposed. This is so chiefly because the normal organisms with which we deal are fully differentiated at the time of, and for that matter, even considerably before birth. It is unnecessary therefore to place emphasis upon processes such as that of tissue differentiation, which at an earlier stage normally accompany and are so closely associated with growth itself that it is not always possible to distinguish or to deal with either of them separately. Consequently, it is quite reasonable to consider the human infant as representing an organized group of various cell populations, and on this basis we shall treat the case of human growth much in the manner of dealing with the simpler example of growth among non-cellular colonies.

The Definition of Growth—The matter of definition is of particular importance chiefly because it has been found necessary to alter slightly but significantly the almost universal opinion that growth is to be defined in the broadest sense as *increase* in size. The latter, to all intents and purposes seems logical enough, and it has thus been adopted by many writers on the subject. An excellent expression of

this view has been given by Julian Huxley wherein he speaks of growth as "a process of self-multiplication of living substance,"² a statement that is evidently quite in accord with the suggestion just previously made to the effect that we shall here treat the human infant as an organization of various cell-populations upon whose reduplication growth is considered in chief part to depend

There has, of course, been perennial conflict as to whether in the human case, for example, size should be measured preferably in terms of length, mass, or even volume, it being clearly impossible to estimate size in terms of cell number. To this particular matter we shall return later, it is more important just now to see that such discussions must always remain somewhat beside the point as long as the definition of growth itself must be held in question, for even though final agreement as to the best measure of size may ultimately be obtained, we would still be left with the impression that growth is, and can only consist of, an *increase* in size

We prefer instead, on the basis of results outlined elsewhere,³ to conceive of growth as associated with a *change* in size rather than to specify that growth consists exclusively of an increase in size. From the practical point of view, of course, it is immaterial whether we speak of the usual form of growth as a change or as an increase in size because the increments accompanying normal growth are obviously positive. But the distinction just noted is important to a clearer understanding of the fundamental factors which together effect, and for that matter control what is commonly called growth. A simple case will illustrate the usefulness of viewing the problem in terms as general as these. We know, for example, that appropriate quantities of suitable food will sustain the growth of a young infant or of some young experimental animal, we know also that abstinence from food cannot be followed by continuous increase in weight, and indeed that the reverse is always true. We are thus confronted with the alternative of calling the positive changes growth, the losses starvation, and the entire scheme something else, as though each of these events were essentially different transactions without bearing upon, or without any relation, save that already mentioned, to each other, or, of taking the simpler position that all changes whether positive or negative, and hence quite independent of food supply at all, are dominated by a single process which succeeds under normal circumstances in producing the result called growth, or under "abnormal" conditions, in traversing with equal certainty the path recognized broadly as starvation. The fundamental phenomenon is thus made to take the name of its more conspicuous subsidiary, whence it is natural to regard the entire affair as a problem in the "motion of growth." Support for this suggestion is found not only in the fact that the actual course of starvation may be predicted from the equations of growth for the case

of complete or even partial removal of food, but also in the fact that the trend of basal metabolism during starvation is just as definitely accounted for as it is during the normal course of growth.²

Thus far, however, we have not defined growth in sufficiently exact terms, for study of the subject clearly reveals that there is something more to the quantitative character of growth than mere change in size, there is, in fact, no difficulty in realizing that the latter description concise as it is, refers, and can refer only to a *difference* in size at two succeeding times, and thus to a gain if the difference be positive, or to an actual loss if the reverse be true. Growth, on the other hand, in its purest form, is intrinsically a matter of cellular reduplication and not one of simple change in cell number. It is, moreover, clearly dependent upon energy exchange, and it is likewise subject, as we have elsewhere shown, to actual dynamical constraints, whence we are easily led to consider all growth a mode of motion the essence of which is held to be *change in size per unit size*.

The capital differences between "true growth" and "ordinary gain" as just described, are set out in Table I where items (2) and (3) represent in mathematical notation the quantities likewise given by items (1) and (4) respectively.

TABLE I
COMPARISON BETWEEN TRUE GROWTH AND ORDINARY GAIN

(1) Definition	GROWTH	GAIN
	Change in Size per Unit Size	Change in Size
(2) Quantity	$q = \int_0^t \frac{1}{s} \frac{ds}{dt} dt = \text{Log. } \frac{s}{s_0}$	$\int_0^t \frac{ds}{dt} dt = s - s_0$
(3) Instantaneous Rate	$\frac{dq}{dt} = \frac{1}{s} \frac{ds}{dt}$	$\frac{ds}{dt}$
(4) Unit of Rate	Kg./Kg./T	Kg./T

The letter *s* represents size in terms of mass, length or cell number

The preceding statements and the data in the table thus emphasize what may be termed the "relativity of growth," a point of view by no means distinctly new for Minot³ as early as 1891 recognized its importance and made the first clearly conceived efforts to compute by approximation what he properly termed 'the rate of growth' and what may also be called in the usual case, the relative rate of gain. The success of more recent investigators, incidentally, in dealing mathematically with certain forms of growth is especially noteworthy in the case of those who employ expressions based upon or directly related to an equation first proposed by Benjamin Gompertz⁴ in 1825, which implicitly takes account of this 'relativity of growth'.

Size—With this particular conception of growth itself in mind, we are next confronted by the traditional problem regarding size. Here, however, greater leeway is permissible, and it may be admitted that the specification of size can, for the most part, be quite properly decided, in the individual case, on the basis of suitability or even of convenience. From the biologic point of view the most generally acceptable measure of size is clearly cell number. This is a unit which may be immediately applied to the case of growth in unicellular populations, though it suffers in the case of the higher forms in part from the fact that not all cells of such an organism are either alike or themselves of identical size. But the greater difficulty in these instances is to count the cells, and we are therefore required to express size in terms either of length or mass. A choice between the two is again purely a matter of convenience, provided we desire to use but *one* of these dimensions, for mass is itself a function of length *via* the property of density, and so long as the latter remains constant it is unimportant from this standpoint alone, whether we determine size as a function of length or of mass. In a complete analysis, and in the most general case where length and mass are understood to vary independently, each will need to be considered, but, since it is always preferable to work as long as possible with a *single* dependent variable, we approach the study of human growth best of all in terms of mass, or for practical purposes, in terms of weight, neither the convenience, nor the precision of which is in any serious doubt. Such procedure is especially allowable where, as in the human case, a certain change in mass at a particular stage of development calls for a corresponding change in length, though the relation between these changes is obviously not, nor does it need to be, uniform over the entire growth epoch.

Metabolism or Basal Metabolism—This useful term has found and indeed in certain respects, deserves the numerous applications it already enjoys. When used alone, however, it refers in general to energy exchange and in particular to that portion of energy which is actually disbursed and can be measured in the form of heat by accepted modern methods of procedure. But heat production, in turn, has been, and in reality requires to be, treated in one of several ways. There are, as a matter of fact, three essentially different units in which heat production may be expressed and for purposes of clarity they are outlined briefly in Table II.

TABLE II
CLASSIFICATION OF BASAL HEAT PRODUCTION

TYPE	UNIT
1 Cumulative Heat	Calories*
2 Rate of Heat Production	Calories per day
3 Rate of Heat Production per unit of size, i.e., True Metabolism	Calories per Kg per day

*The large or Kg Calorie

The term metabolism, if it is to be useful at all, can obviously not apply to each and every one of these three units of heat output in elusively, primarily because it is intended, whether so expressed or not, to convey a decidedly more restricted and definite impression than that contained in the comprehensive phrase "heat production." Consequently, in order to avoid misunderstanding, it is suggested that the unit of heat production given in item 3 of the table, be accepted as defining the term metabolism when the latter is used alone in connection with basal heat production.

Thus, so long as mass is chosen in place of length as the more appropriate measure of size in dealing with growth, it is correspondingly preferable in the case of human metabolism to employ the unit expressed in *Calories per Kg per day* rather than to turn obliquely away from the original scheme of things in order to record heat output in terms of surface area. The latter method has been, and continues to be, widely employed in practice, chiefly on the basis of a long and truly serviceable tradition. But it possesses indubitably the serious disadvantage of propagating the entirely false impression that surface area bears a direct causal relationship to heat production. In the extensive discussions which have appeared on the subject arguments *pro* and *con* have been presented with equal fervor, though it is quite immaterial whether surface, mass, or even length are employed as the base of reference, since all of these are explicitly connected by means of the property of matter, called density. The latter, as D. E. Zoellner has recently shown, remains sufficiently constant throughout life to be treated so. Besides the transformation from Cal/Kg/Day to Cal/sq.M/Day is a perfectly simple procedure, and the formulas of Meeh, Lissauer and of others as well as any success to which they are entitled to lay claim depend though the fact is not everywhere recognized, upon the form of this fundamental physical relationship of mass length and density. But so long as mass is the unit of choice in the matter of growth—so long as growth itself is dynamically responsible for the peculiarities of heat production in infants and children, and so long as it is held desirable to determine the quantity of heat relative both to size and to time—there is to be consistent, more reason to express the results with reference to weight than to surface area, even though weight must be acknowledged to 'vary' more widely than body surface when individual children are compared.

It is indeed on just the latter account that standardization on the basis of surface has found much of its favor in modern practice. Now, in view of the physical relations already noted, a given change in mass is bound to be accompanied by a comparatively small change in body surface density remaining the same, whence it is clear that measurements referred to surface as a standard must in the nature of things be expected to appear more uniform and therefore less irregu-

lates to the several forms in which energy is disbursed during the process of growth, the second to the matter of defining the sense with which the term maintenance is employed

So far as the former of these two points is concerned, it may be seen from the chart that the energy supplied for growth is held to be distributed and utilized in five essentially different ways (1) new cells, (2) storage, (3) momentum, (4) dissipation, and finally (5) in the process of synthesis or cellular proliferation, the subjoined characters V_c , κ , λ , ρ , E_c , denoting respectively the several terms in the original equations of growth and metabolism³ that are concerned with the energy partition just mentioned*. But it is also important to know, even from the clinical side of the matter, that these symbols represent in reality, certain fundamental properties of growth, or perhaps better, of the entire system which is undergoing growth. Thus, to take but one example, the symbol ρ represents what we have termed the *resistance to growth*. It is associated, in virtue of this property with energy that is dissipated during the process of reduplication, by which we mean that such energy cannot be recovered to do any further work of growth. Energy so consumed moreover is ultimately liberated in the form of heat and it becomes, as a result, a major factor in the matter of metabolism. Thus, as the chart indicates, the resistance ρ constitutes one of the main connecting links between the events of pure growth on the one hand and heat production on the other.

But an even more important reason why it is necessary to take cognizance of this and of the other symbols is that no satisfactory understanding of growth can be obtained until we are informed precisely how any factor known to affect growth itself, likewise and in turn operates on the various properties of the system schematically arranged and symbolized in the figure. It is evident therefore that growth is insufficiently described, or understood, by merely detailing successive changes of size with respect to age. Accordingly, to get to the bottom of things we shall need to learn not only that some substance, x say, "promotes" or "fails to promote" growth, but we shall actually be required to find out precisely how this substance or factor x affects each of the foregoing fundamental properties of growth as well. To collect this information it is necessary, as the present scheme briefly suggests, simply to study growth on the one hand with concomitant heat production on the other. Such problems, of course, are quite definitely a matter of further research, yet, it seems logical that those who are intimately and primarily concerned with human growth should also be made aware of their importance.

Energy of Maintenance—It has been the custom of pediatricists to speak broadly of the maintenance requirement as that quantity

*A further description of the above symbols as well as a synopsis of other mental quantities entering the equations of motion appears in a current paper.

cause size, either as weight or surface enters the equations of metabolism in such a way as to affect the end results adversely. Greater uniformity is not only to be expected in, but is actually displayed by, observations on heat production which are expressed in the simpler unit of Cal/Day. The latter phenomenon is of particular interest here because it can be strikingly demonstrated in data on the heat production of infants and young children.

THE SCHEME OF ENERGY EXCHANGE FOR GROWTH AND METABOLISM

Having thus considered a number of the more important propositions that are fundamentally in the background of any discussion on

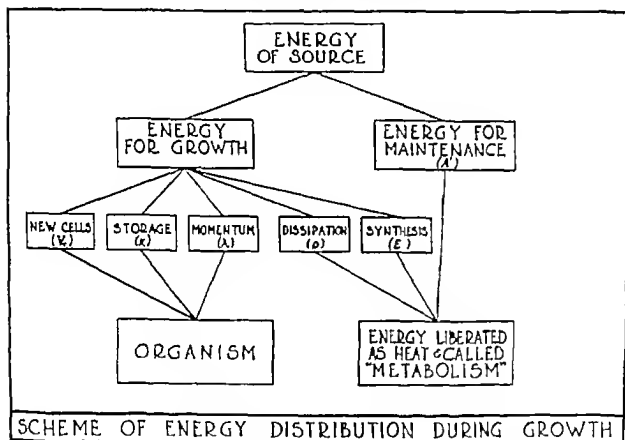


Fig 1.

human growth, it will be useful to outline briefly the scheme of energy exchange by means of which it is possible more clearly to understand many otherwise occult phenomena of growth itself, and upon which in terms of our own analysis, the dynamical connection between growth and metabolism may be said to rest. The procedure itself is simple and is illustrated diagrammatically in Fig 1. It is based primarily upon the fundamental assumption quite easily justified by the conservation law, that an infant let us say in the basal state requires energy for the dual purpose of growth and maintenance alone. There are two respects in which this scheme differs from previous interpretations and special emphasis needs for the sake of clarity to be placed upon them here. The first as is obvious from the figure re-

lates to the several forms in which energy is disbursed during the process of growth, the second to the matter of defining the sense with which the term maintenance is employed

So far as the form¹ of these two points is concerned, it may be seen from the chart that the energy supplied for growth is held to be distributed and utilized in five essentially different ways (1) new cells, (2) storage, (3) momentum, (4) dissipation, and finally (5) in the process of synthesis or cellular proliferation, the subjoined characters V_c , κ , λ , ρ , E_c , denoting respectively the several terms in the original equations of growth and metabolism² that are concerned with the energy partition just mentioned*. But it is also important to know, even from the clinical side of the matter, that these symbols represent in reality, certain fundamental properties of growth, or perhaps better, of the entire system which is undergoing growth. Thus, to take but one example, the symbol ρ represents what we have termed the *resistance to growth*. It is associated, in virtue of this property with energy that is dissipated during the process of reduplication, by which we mean that such energy cannot be recovered to do any further work of growth. Energy so consumed moreover is ultimately liberated in the form of heat and it becomes, as a result, a major factor in the matter of metabolism. Thus, as the chart indicates, the resistance ρ constitutes one of the main connecting links between the events of pure growth on the one hand and heat production on the other.

But an even more important reason why it is necessary to take cognizance of this and of the other symbols is that no satisfactory understanding of growth can be obtained until we are informed precisely how any factor known to affect growth itself, likewise and in turn operates on the various properties of the system schematically arranged and symbolized in the figure. It is evident therefore that growth is insufficiently described, or understood, by merely detailing successive changes of size with respect to age. Accordingly, to get to the bottom of things we shall need to learn not only that some substance, x say, "promotes" or "fails to promote" growth, but we shall actually be required to find out precisely how this substance or factor x affects each of the foregoing fundamental properties of growth as well. To collect this information it is necessary, as the present scheme briefly suggests, simply to study growth on the one hand with concomitant heat production on the other. Such problems, of course, are quite definitely a matter of further research, yet, it seems logical that those who are intimately and primarily concerned with human growth should also be made aware of their importance.

Energy of Maintenance.—It has been the custom of pediatricists to speak broadly of the maintenance requirement as that quantity of

*A further description of the above symbols as well as a synopsis of other fundamental quantities entering the equations of motion appears in a current paper³.

energy necessary at any stage of infancy or childhood to prevent loss of body weight, and consequently as that quantity sufficient for all purposes (including activity and waste) other than that of growth itself. Now, discounting the fractions recently classified as "super metabolism," i.e., food, activity and temperature,⁴ a similar interpretation can be made to apply to the basal state. Consequently, since basal metabolism (Cal/Kg/Day) is actually higher in infancy than in childhood, it is clear that 'maintenance needs' in the sense described above, will likewise decline as age advances and as the "impetus" of growth becomes less. On a comparative basis an older child in the basal state will therefore require less energy than an infant to keep from losing weight. This particular interpretation of "maintenance" fills a useful place in practice but it has been found necessary, in dealing with growth and metabolism from the dynamic point of view, to look upon this question of maintenance somewhat differently.

True maintenance from the latter standpoint, can and should be held to apply only to tissue that is physiologically at rest and that is to tissue in a state of pure and simple existence. Thus, tissue which is in a state of growth is not considered as being 'at rest' it is, as a matter of fact, "in the motion of growth," though quite evidently, just as much in need of being nourished as though it were not. Its energy requirement will, obviously, and for the reason just mentioned be more than that of an equal quantity which remains 'at rest' and it is evident, therefore, that maintenance so defined refers solely to the quantity of energy required to keep the cells in nutritional equilibrium. The proposition here involved could be put forth in another way by stipulating that comparisons of maintenance energy should be calculated for tissues in the same state of activity whence for obvious reasons, it would be simplest to select the state of 'rest' as the most suitable base of comparison. Thus, basal heat output well known to be high in infancy and throughout childhood we shall consider high solely because it is generated by tissue which is naturally in a different state of activity at this than at a later stage of life, and the difference will be held to the account of growth itself. These relationships are most simply portrayed by means of the self-explanatory scheme already presented in Fig. 1.

From this it is clear first that basal heat production in growing subjects must always exceed that of subjects in whom growth has ceased and second that the comparatively higher metabolism and the relatively greater energy requirement of healthy infants and children is due and due only to the fact that they are immersed in the flux of growth.

It may finally be understood on the basis of the present conception of growth and from the foregoing definition of maintenance how the restriction of food to the level of maintenance requirements alone

(25.34 Cal /Kg /Day) will necessarily be followed by a course of swift and unescapable loss of weight in a subject undergoing growth, and how, on the contrary, another subject who has come to the stage of adult equilibrium and is given an equivalent quantity of food, will incur no loss at all

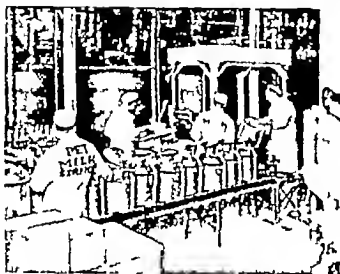
REFERENCES

- 1 T. Lucretius Carus De Rerum Natura, II 1 1121
- 2 Spencer, H The Principles of Biology, New York, 1909, D Appleton & Co
1 141
- 3 Wetzel, N C Proc Soc Exp Biol and Med 30 224, 227, 233, 354, 358, and
360, 1932
- 4 Huxley, J S Problems of Relative Growth, New York, 1932, The Dial Press,
p 6
- 5 Minot, C S J Physiol 12 97, 1891
- 6 Gompertz, B Phil. Trans Roy Soc., p 513, 1825
- 7 Zook, D E Am J Dis Child 43 1347, 1932
- 8 Growth and Development of the Child, White House Conference Report, Part III,
Nutrition, New York, 1932, The Century Co, p 339
- 9 Wetzel, N C Proc Soc Exp Biol and Med 30 1044, 1933

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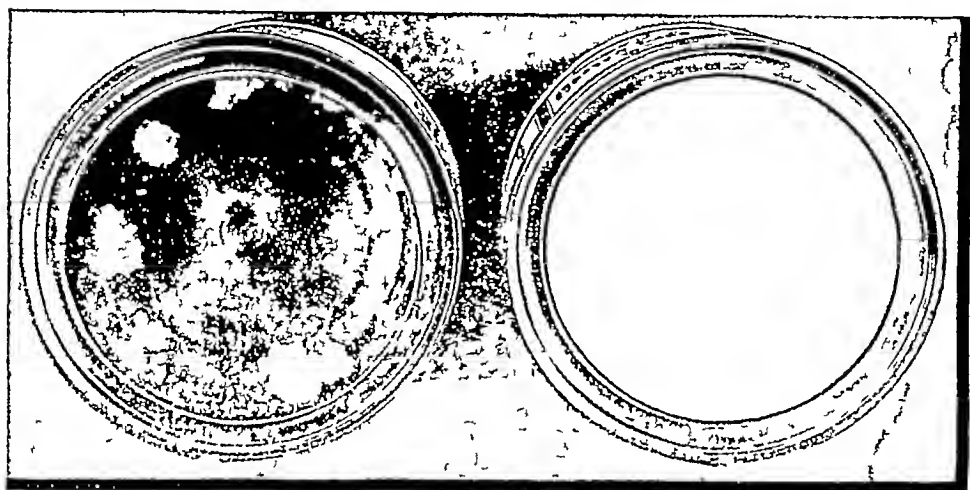
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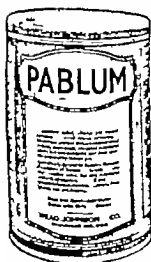
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Copper	0.0013	0.0005	0.00017	0.00034	0.000015	0.00023	
Vitamin A	+	— to +	—	— to +	++ +	++	
Vitamin B(B ₁)	++ +	++ +	+	+	+	+	
Vitamin C	—*	—*	—*	—*	—*	—*	
Vitamin D	—**	—**	—**	—**	—**	—**	
Vitamin E	++ +	++	—	—	— to +	+	
Vitamin G	++ +	+	— to +	+	++	+	
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